The Impact of Leprosy Control

Epidemiological and modelling studies

Abraham Meima

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De invloed van leprabestrijding

Epidemiologische en modelmatige studies

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Abraham Meima

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Promotor: Prof. dr. ir. J.D.F. Habbema

Overige leden: Prof. dr. A. Hofman
                  Prof. dr. W.C.S. Smith
                  Prof. dr. H.A. Verbrugh

Copromotor: Dr. ir. G.J. van Oortmarssen

voor Sander

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Introduction

This thesis consists of studies addressing the impact of leprosy control activities on the occurrence of leprosy and its impairments. Assessing this impact is difficult because the epidemiology of leprosy is fraught with uncertainties. Knowledge of processes governing leprosy transmission is limited, and controlled studies enabling direct assessment of the impact of interventions on transmission have never been conducted. Nevertheless, decisions regarding the extent and organisation of leprosy control programmes need to be made. This applies in particular to the present era, which has witnessed drastic epidemiological improvements in some developing countries, but no change in others.

This introductory chapter provides a background to the studies presented in Chapters 2-8. First, essential knowledge of leprosy infection, disease and its consequences, and transmission is summarised (1.1). Next, the history of leprosy control and available control options are described briefly (1.2). Section 1.3 summarises patterns in the global occurrence of leprosy and related health problems from 1985 onwards. Section 1.4 introduces our epidemiological modelling approach for investigating the potential impact of leprosy control, and summarises earlier modelling work. Finally, the research questions of this thesis and outlines of the chapters are given (1.5).

1.1 Leprosy

Leprosy is a chronic infectious disease which affects the peripheral nerves and the skin. It is often referred to as 'the oldest disease known to man' (*1*). The earliest written records describing leprosy come from India and date back to about 600 BC. The earliest remains of people confirmed to be affected with leprosy stem from Egyptian excavations which disclosed leprous skulls buried in the second century BC.

Infection and disease

Leprosy is caused by the bacillus *Mycobacterium leprae*. This bacillus was one of the first agents to be linked to an infectious disease. *M. leprae* was discovered in 1873 by Hansen in a Norwegian leprosy research hospital (*2*). Despite this early discovery, leprosy is even today a disease which is not well understood. The inability to culture *M. leprae* is an important reason.

Establishing leprosy infection is difficult. A recent study which employed serological testing indicated leprosy infection to be far more common than leprosy disease (*3*), which confirms suggestions from the 1980s (*4, 5*). In recent years, considerable progress has been made in the development of diagnostic tools for leprosy infection, including skin and serological tests and molecular polymerase chain reaction tests (*3*). Still, it is not possible to predict who will develop leprosy disease and who will not. Genetic factors appear to influence resistance to leprosy infection and to development and expression of disease (*6*), but the importance of these factors is unclear.

The duration of the incubation period of leprosy is also uncertain. Estimates were made for American and English war veterans who served in areas endemic for leprosy and later

developed leprosy disease (*4*). The estimated duration ranged from half a year to 21 years. It has been suggested that disease may not only develop after primary infection, but also from endogenous reactivation of dormant bacilli acquired earlier in life (*5*).

In this thesis, leprosy disease refers to presence of signs that can be diagnosed through physical examination. Disease manifestations vary widely because cellular responses which constitute the body's main defence against *M. leprae* vary strongly between individuals (*4*). Previously, the most common classification system used was the Ridley-Jopling system which recognises a spectrum with five groups and an 'indeterminate' class. Cellular immunity is strong at one end of the spectrum (polar tuberculoid leprosy, or TT), and absent at the other end (polar lepromatous leprosy, or LL). Skin and nerve lesions caused by leprosy have few bacilli at the tuberculoid, and many bacilli at the lepromatous side of the spectrum. Microscopic examination of skin smears for bacilli is often applied as an additional diagnostic procedure for classifying leprosy patients (i.e. those with signs of leprosy). A considerable proportion of tuberculoid patients may heal spontaneously. The three intermediate groups of the Ridley-Jopling system are referred to as borderline leprosy (BT, BB and BL). Movements of patients across the leprosy spectrum occur, and borderline leprosy is much less stable than the two polar forms of leprosy (TT and LL).

Transmission

The discovery of *M. leprae* in 1874 disproved the hereditary theory of leprosy. But even today the debate about the mode of transmission of *M. leprae* is not closed. Leprosy is considered to be transmitted almost exclusively within the human population. The two most common hypotheses for leprosy transmission are skin-to-skin contact and airborne transmission, with discharge of bacilli from the nasal mucosa of infectious individuals and entry of bacilli through the respiratory tract (*6*). Nowadays most leprologists favour the airborne hypothesis, which is supported by several observations: nasal excretion of leprosy bacilli is much more common than from any other part of the body in leprosy patients and untreated lepromatous patients excrete large numbers of bacilli from the nose (*7*). Also, occurrence of *M. leprae* DNA in the nose of healthy individuals has been shown to be widespread in leprosy endemic populations (*3*).

The question of who is to what extent contributing to transmission remains unresolved. Traditionally, lepromatous (LL) patients were thought to be the main source of infection. But compared to the general population, the risk of developing leprosy is also considerably higher for household contacts of non-lepromatous patients (*8-10*). This may in part be due to common sources of infection outside the household. The idea that patients are the only source of infection is currently being challenged. Individuals incubating for leprosy disease could transmit leprosy, for there is no reason why the shedding of bacilli would start only with the onset of signs of leprosy disease, which involve nerve and skin. A possibly important role for self-healing infections which do not result in disease, but which do have a transient period of nasal excretion, has also been suggested. It can therefore not be excluded that transmission by leprosy patients may be

less important than transmission by those who do not (yet) have any signs of the disease (*7*). Transmission may also be indirect: transmission through insect bites can for instance not be excluded (*11*). Finally, animal sources (e.g. armadillos) and environmental sources of infection (e.g. soil, water) may possibly be relevant for the persistence of leprosy (*12*).

Socio-economic conditions

A review of international literature suggested that socio-economic conditions play an important role in leprosy (*11*). Declines in numbers of new patients are thought to be related to socio-economic improvement. Several factors that may play a role have been identified: housing conditions, number of persons per household per room, family size, nutrition and schooling.

Impairment and disability

Mild self-healing forms of leprosy with only one single skin lesion do occur, but leprosy can also be a chronic and destructive disease. Leprosy is a public health problem because it may cause impairment, and subsequently, disability and handicap. Impairment is related to the preference of *M. leprae* for peripheral nerves. The initial signs of leprosy are skin lesions and/or neuritis (nerve thickening, tenderness and pain) and/or nerve function impairment (loss of motor, sensory or autonomic nerve function). Nerve function impairment can develop before initiation of chemotherapy, during this treatment, and even after its completion. New nerve function impairment can develop silently (i.e. no spontaneous complaints of nerve pain, paraesthesia and/or nerve tenderness on palpation), but can also be part of a clinically apparent reversal reaction (RR) or erythema nodosum leprosum (ENL) reaction (*13*). High bacillary loads within nerves of lepromatous leprosy patients may in itself also cause nerve function impairment (*14*).

Nerve function impairment is a primary complication of leprosy as it is directly associated with *M. leprae*. Secondary complications include plantar and palmar ulceration, contractures of digits, stiffness of joints, and disintegration of bones of hands and feet (*15*). Secondary complications may be caused by unprotected use of hands and feet with nerve function impairment. Peripheral nerve damage may also cause lagophthalmus (inability to close the eye lid) with corneal ulceration and subsequent blindness as possible secondary complications.

A grading system is employed to measure the severity of impairment. This system evolved over time, and was last revised in 1998 (*16, 17*). A grade of 0-2 is assigned to each of six body sites (both eyes, hands and feet; Table 1.1), and an overall grade for a patient is determined as the maximum of these six grades. The grades are a composite measure for nerve function impairment and secondary complications. They are often referred to as 'WHO disability grades' instead of the more appropriate 'WHO impairment grades'. Many leprosy control programmes provide information on impairment in their routine reports, but usually only the proportion and number of new patients with overall grade 2 are provided.

Table 1.1 WHO grading system for measuring the severity of impairment for hands, feet and eyes.

	Hands and Feet
Grade 0	No anaesthesia, no visible deformity or damage
Grade 1	Anaesthesia present, but no visible deformity or damage
Grade 2	Visible deformity or damage present
	Eyes
Grade 0	No corneal anaesthesia; no evidence of visual loss
Grade 1	Corneal anaesthesia; vision not severely affected as a result [a]
Grade 2	Vision severely affected due to leprosy and/or lagophtalmos and/or iridocyclitis and/or corneal opacities [a]

[a] Vision is considered severely affected in case of inability to count fingers at six metres or if vision is less than 6/60.

Due to impairment, patients may develop disabilities and handicaps: it may become difficult or even impossible for someone to carry out activities necessary for daily life and income generation. For instance, manual dexterity may be affected because of insensitivity and muscle paralysis. Walking may become difficult or impossible because of ulcers or disintegration of bones of the foot. Limitations in eye sight may hinder orientation in space, mobility and many other aspects of living. A further consequence is that a disabled individual may experience disadvantages that limit or prevent fulfilment of his or her normal role in society (handicap). Ultimately, leprosy patients may lose social status and become progressively isolated from society, family and friends (destitution). The gross deformities which used to be encountered regularly in neglected leprosy patients, contributed to the social stigma which is still attached to the disease.

1.2 Leprosy control

The various dimensions of leprosy are addressed by specific interventions. Early detection of patients is essential for preventing impairment. Subsequent chemotherapy cures patients bacteriologically, and as a secondary effect may reduce transmission. Other measures that may reduce transmission will be described below. Timely detected nerve function impairment can often be recovered through treatment with corticosteroids. Impaired and disabled patients may receive physiotherapy, and aids and appliances such as protective footwear, gloves, splints, spectacles and modified tools. Reconstructive and plastic surgery can be offered to patients with deformities of hands, feet or face. Measures such as vocational training and sheltered workshops aim at rehabilitation of leprosy patients. Finally, health education of the public, for instance through mass media, creates awareness of early signs of leprosy, and aims to change attitudes towards leprosy and leprosy patients.

Chemotherapy-based control

For centuries, leprosy 'control' consisted of measures for segregating leprosy patients from the general community. Isolation undoubtedly nurtured the stigma attached to leprosy (*4*). In the 1940s, dapsone (DDS or diaminodiphenyl sulfone) was found to be an effective drug for treating leprosy patients. Being cheap and not very toxic, dapsone monotherapy soon became the mainstay of leprosy control programmes around the world (*4*). With the introduction of domiciliary treatment regimens, a trend away from institutionalisation of patients was encouraged. Dapsone is thought to quickly remove the infectiousness of patients (*18*). Supposedly, this would lead to reductions in levels of leprosy transmission. However, the initial optimism of conquering leprosy within the foreseeable future turned into frustration. Dapsone often required long term or even life-long treatment, which led to poor patient compliance (*19*). Negative social attitudes towards leprosy and leprosy patients complicated case detection (i.e. the detection of new leprosy patients) and treatment compliance. In addition, treatment became increasingly ineffective due to widespread development of secondary resistance of *M. leprae* – i.e. resistance acquired as a result of inadequate treatment – against dapsone. Low dosages of dapsone and low compliance predisposed the development of secondary resistance (*18*). Dapsone resistance in previously untreated patients (primary resistance) was also found frequently. This type of resistance probably results from infection with drug-resistant organisms that originate from another patient with secondary resistance. Most primary resistant patients had a low degree of resistance: they were still expected to respond to treatment with dapsone in full dosage (*20, 21*). Nonetheless, by the early 1980s it was clear that dapsone monotherapy was steadily losing its usefulness.

In the 1960s, the availability of better drugs, including rifampicin which is highly bactericidal, made treatment through combinations of drugs possible (*22*). The rationale for using multiple drugs is to prevent development of resistance: mutant bacilli that are not sensitive to rifampicin will be killed by one of the other drugs. In 1981, the World Health Organization (WHO) recommended to treat leprosy patients with a standard multidrug therapy regimen including rifampicin (MDT). Although more expensive than dapsone, MDT has important advantages: (a) relatively short duration of treatment; (b) low relapse rates following completion of treatment; (c) so far, there is no evidence of treatment failures attributable to drug resistance. Toxicity of dapsone and MDT is not a problem, although side-effects occur occasionally.

MDT is provided free of charge and is very well accepted by national health services (*19*). The introduction of MDT also contributed to improvements in the organisation of leprosy control. A quick cure contributed to earlier self-reporting, and to better treatment compliance. Ultimately, the social stigma attached to leprosy may even be reduced through increasing awareness of its curability (*23*). MDT was implemented gradually: in 1993, 49% of patients worldwide under treatment were reported to receive MDT (*24*), versus 99% in 1998 (*25*). As with dapsone, the advent of MDT raised great optimism in at least part of the leprosy community. It was suggested that "through early diagnosis and

effective treatment, the transmission of the disease could virtually be stopped over a period of time" (*19*). However, such an impact has not yet been demonstrated. Assessment of the impact that chemotherapy-based control has on leprosy transmission is one of the objectives of this thesis.

For treatment with MDT, patients are classified into paucibacillary (PB) and multibacillary (MB) leprosy. Initially, patients were assigned to PB and MB on the basis of the Ridley-Jopling system and results of skin smear testing. In 1998, it was concluded that patients could be classified on the basis of skin lesion counts, which led to new definitions of PB and MB leprosy (PB: 1-5 lesions, MB: more than 5 lesions) (*17*). PB patients are to be treated with two drugs (rifampicin and dapsone) for a period of six months (*26*). MB patients receive three drugs (rifampicin, dapsone and clofazimine). The recommended duration of treatment for MB leprosy was gradually shortened: from "at least two years, and ... whenever possible, until skin smears negativity" (*26*), to 24 months (*27*), to 12 months (*28*). Nowadays, WHO also considers a single dose of a different regimen, ROM (rifampicin, ofloxacin and minocycline), acceptable as an alternative for the treatment of single-lesion PB leprosy in programmes which maintain strict diagnostic criteria and which detect very large numbers of such patients (*28*). WHO does not recommend use of ROM for single-lesion PB leprosy in other programmes, because catering to a third regimen (ROM) would complicate logistics and information systems, and because use of ROM may lead to over-diagnosis of non-leprosy skin patches as leprosy. WHO has been criticised for simplifying the management of leprosy through the discontinuation of smears and the shortening of the recommended treatment duration for MB patients, without conducting thorough scientific research (*29*). In 2002, it was proposed to study the effectiveness of uniform treatment of PB and MB patients for a period of six months with the standard MB/MDT regimen (*30*).

Immunoprophylaxis and chemoprophylaxis

The use of BCG (Bacille Calmette-Guérin) vaccination for tuberculosis (TB) dates back to the 1920s. TB is also caused by a mycobacterium, *M. tuberculosis*. BCG was incorporated in the Expanded Programme on Immunization's (EPI) infant vaccination schedule in 1974 as a preventive measure against tuberculosis. The rationale for this is that BCG protects against serious childhood forms of tuberculosis; its protective efficacy against adult pulmonary forms of tuberculosis varies widely in different parts of the world (*31*).

BCG may also be valuable for leprosy control. In randomised controlled trials (RCTs), the efficacy of BCG in preventing leprosy ranged from 20% to 80%, with low values in South-East Asia (*32, 33*). It is unclear whether, and to which extent, BCG's protective efficacy against leprosy wanes with time. A trial from Venezuela and another RCT in Malawi showed that the protective efficacy of BCG against leprosy is enhanced with repeated administration (*34*). However, the Malawi RCT showed an association between

revaccination and increased risk of tuberculosis in HIV-infected individuals, prohibiting mass revaccination campaigns.

Recently, other vaccines have also been tested. A RCT in South India demonstrated two vaccines, ICRC and BCG plus heat-killed *M. leprae*, to have higher protective efficacy than BCG (*35*). On the other hand, the Malawi RCT and the Venezuela trial failed to show evidence that the addition of killed *M. leprae* enhances the protective efficacy of BCG (*34*).

So far, trial results for leprosy have had little effect on vaccination policies. An exception is the policy of repeat BCG vaccination of contacts of leprosy patients, that is routinely carried out in some places (*34*). In most countries, BCG is only administered at birth (or at the first contact with the health services) (*31*). The estimated worldwide coverage of infant BCG vaccination gradually increased from 15% in 1980 to around 80% throughout the 1990s (*36*). The protection imparted by BCG also has an indirect effect: those who are prevented from developing leprosy will also not transmit leprosy to others. It has been claimed that BCG has been a factor in the decline of leprosy in certain populations (*37*). However, the proportion of leprosy patients that has been prevented by BCG up till now is probably rather low because (a) in most countries, only infants are vaccinated; (b) children usually constitute only a minority in the detection of leprosy; (c) the protective efficacy of BCG may wane with time; (d) BCG coverages may have been low, especially in the 1980s. The latter implies that the proportion of present adult populations ever having received BCG will in general be low. In this thesis, the impact of BCG vaccination of infants on leprosy transmission is explored along with the investigation of the impact of chemotherapy-based control.

The possibility of chemoprophylaxis using dapsone or a derivative, acedapsone, in the prevention of leprosy has been investigated extensively. The protective efficacy of treatment ranged from 34% to 54% in a meta-analysis of five RCTs in which household contacts of leprosy patients were followed (*38*). The protective efficacy of (ace)dapsone prophylaxis was suggested to be around 60% when studies with other designs were considered as well. Increasing dapsone resistance in the 1970s prohibited further development of dapsone-based chemoprophylaxis policies. The scientific interest for chemoprophylaxis disappeared largely in the 1980s and 1990s following the introduction of MDT, but revived in recent years. This is mainly due to the fact that global case detection rates of leprosy have remained stable throughout the 1990s (see section 1.3), and associated concern that MDT may not be sufficient to interrupt the transmission of leprosy. To date, chemoprophylaxis is not part of routine leprosy control programmes. A drawback of prophylactic treatment with dapsone in addition to resistance was the duration of treatment: in some of the RCTs, the treatment duration was several years. The efficacy of prophylactic treatment using only a few doses of newer drugs is not well known. Only one study was conducted: single dose rifampicin was given to a remote island population in French Polynesia in 1988. The estimated efficacy of this mass intervention was 40-50% (*38*). To further investigate the impact of chemoprophylaxis, two studies using two prophylactic doses of either ROM (rifampicin, ofloxacin and

minocycline; first study) or rifampicin (second study) were started in island populations in 1996 and 2000 (*39, 40*). In addition, two randomised controlled trials using single dose rifampicin in contacts of leprosy patients started in 2000 and 2002, respectively (*41, 42*).

1.3 Global situation

Leprosy control programmes routinely provide information on the number of patients detected, the percentage of new patients presenting with WHO grade 2 impairment, and the total number of patients who are registered within the programmes. Aggregated information from 1985 onwards is summarised below.

Published trends in annual case detection vary widely between areas. A systematic review of these trends was lacking (what are the exact trends?, can they be explained?), and is presented in this thesis. Despite of the wide variability between areas, the global annual case detection trend over 1985-2000 was rather constant, except for an elevation in 1998-2000 (*43, 44*). On average, about 650,000 cases were detected per year in the period 1990-2000. Table 1.2 provides a breakdown of global case detection by WHO Regions and countries for the year 1998.

Of the seven million new patients detected globally during 1985-1996, 550,000 (8%) presented with WHO grade 2 impairment (*45*). The percentage with WHO grade 2 decreased from 10% in 1985 to 7% in 1995 and 4% in 2000 (*44, 45*). Due to possible underreporting of cases with impairment and overdiagnosis of leprosy, the actual percentages of new patients with grade 2 impairment at the time of detection may have been higher, especially in most recent years.

The number of individuals living with impairment caused by leprosy has not been monitored systematically. By consequence, only crude estimates are available about the number of individuals living with impairment caused by leprosy, which reflects the impact that leprosy has on public health. In 1995, WHO estimated the number of individuals with impairment caused by leprosy to be between one and two million (*46*). In 1998, the Seventh WHO Expert Committee On Leprosy mentioned that "there may be about three million persons with leprosy-related impairments and disabilities in the world, including about two million with grade 2 disabilities and about one million with grade 1 disabilities" (*17*). The number of individuals living with impairment depends on how many patients who were detected in the past already had impairment at the time of their detection, on changes in the impairment status of patients during chemotherapy treatment and after release from treatment, and on survival probabilities. The presence of impairments at the time of detection is believed to be associated with longer delays between onset of disease and detection. Both this association and the occurrence of changes in the impairment status of patients during and after treatment are investigated in this thesis.

In leprosy, the number of patients in registers of control programmes is denoted as 'prevalence' or 'registered prevalence'. The trend in global registered prevalence since 1985 contrasts sharply with the case detection trend. The registered prevalence fell almost

Table 1.2 Case detection for countries with at least 2000 detected cases, for the WHO Regions and global case detection, 1998.

Country / region [a,b]	Cases detected in 1998	Contribution to global case detection (%)	Country / region [a,b]	Cases detected in 1998	Contribution to global case detection (%)
Africa			*South-East Asia*		
Ethiopia	4,457	<1%	Bangladesh	12,351	2%
Guinea	3,684	<1%	India	634,901	79%
Madagascar	8,957	1%	Indonesia	18,367	2%
Mozambique	3,764	<1%	Myanmar	14,357	2%
Niger	2,549	<1%	Nepal	6,570	<1%
Nigeria	7,230	<1%	Other countries	2,523	<1%
Tanzania	3,535	<1%	Total	689,069	86%
Other countries [c]	17,354	2%	*Western Pacific*		
Total	51,530	6%	China	2,051	<1%
Americas			Philippines	3,490	<1%
Brazil [d]	42,055	5%	Viet Nam	2,162	<1%
Other countries	5,163	<1%	Other countries	2,914	<1%
Total	47,218	6%	Total	10,617	1%
Eastern Mediterrenean					
Sudan	2,077	<1%	*World*		
Other countries	3,846	<1%	Total	804,357	100%
Total	5,923	<1%			

[a] Less than 100 cases were reported in Europe.
[b] Case detection figures for countries were taken from (*47*) and for WHO Regions and global case detection from (*44*). Case detection figures for "other countries" were derived from the figures for the WHO Regions and listed countries.
[c] Case detection in the Democratic Republic of the Congo exceeded 2000 cases; exact information is not available.
[d] The case detection figure for Brazil was taken from (*43*).

everywhere in the world (*43, 48, 49*). Overall, the fall was dramatic: from 4.0 million patients in 1985 to 750,000 around the year 2000 (*43*). There are two important reasons for this fall. Firstly, there was no consistency in register keeping: following the introduction of MDT, many (ex-)patients not in need of chemotherapy, but possibly with impairments or disabilities, were removed from programme registers (*29, 50*). Secondly, patients became registered for shorter periods of time, simply because MDT has a much shorter treatment duration than dapsone. 'Registered prevalence' is often incorrectly used as a synonym for the number of leprosy patients receiving chemotherapy; 'on-treatment

prevalence' is a more correct term. The detection figures illustrate that the fall in registered prevalence is *not* due to decreases in case detection.

In 1991, the World Health Assembly (WHA) set a target to "eliminate leprosy as a public health problem". This target was defined as an on-treatment prevalence of less than 1 per 10,000 population, and was announced achieved at a global level in May 2001, despite of the fact that global case detection did not fall. Recently, WHO was criticised heavily for its emphasis on the elimination target; there is no evidence that reaching the target will result in transmission reductions (*29*). It is feared that proclaiming of achievement of the elimination target will result in loss of commitment and resources for leprosy control programmes. In the year 2000, WHO scheduled that the elimination target would be reached at national level in all countries by the end of the year 2005 (*51*). It remains to be seen whether this goal will be achieved, and what the role will be of operational factors which do not affect leprosy transmission. For instance, treating more single lesion leprosy cases with single dose ROM instead of MDT (see section 1.2) will reduce the on-treatment prevalence, but will not affect transmission and case detection.

1.4 Modelling approach

The impact of interventions on trends in the transmission of leprosy over time can be assessed by analysing intervention studies and programme registries. Proper statistical assessment is very difficult however, due to limitations of the available datasets in combination with epidemiological features of leprosy, as is explained below. We therefore developed an epidemiological framework for modelling leprosy transmission, which plays a key role in this thesis and builds on earlier modelling work for tuberculosis and leprosy. In this section the rationale for the modelling approach is provided, and earlier modelling work is addressed.

Limitations of leprosy intervention studies and programme registries

Various intervention studies, such as studies into the effectiveness of MDT in curing patients, and RCTs for BCG vaccination and chemoprophylaxis, established the effectiveness of interventions for leprosy at the individual level. Extrapolation of the study results to assess the impact of the interventions on trends in transmission in populations is difficult for several reasons. In RCTs, there were no areas with and without the intervention, because randomisation was not by geographical area. In addition, routine leprosy control activities were continued during intervention studies, which may have blurred the effects of the study interventions on transmission in the study area. Also, the study periods of the studies were not sufficiently long, which is a problem because changes in leprosy transmission in populations only unfold gradually, due to the long and variable incubation period of leprosy. Studies designed to determine how interventions that have been proven beneficial at individual level affect trends in transmission have never been conducted. This is not surprising: not only would such studies be very costly due to the long study period needed, it is also not ethical to withhold interventions that

have been proven beneficial at individual level from study populations in intervention studies.

Related issues complicate the assessment of the impact of interventions on trends in transmission on the basis of longitudinal data from leprosy control programmes. In interpreting downward trends in case detection (the closest proxy indicator for transmission), competing explanations must be considered: both chemotherapy-based control and BCG vaccination may have contributed, and socio-economic conditions may have improved. Disentangling these explanations with statistical techniques (e.g. regression analysis, time-series analysis) is difficult, especially because this would require datasets that describe long-term trends in geographical areas with comparable general conditions, but with different well-documented interventions. We could not identify such datasets. In addition, variability in control efforts and methods over time must be taken into account when interpreting observed case detection trends. For instance, leprosy control activities were intensified both in the early and in the late 1990s (*45, 52*), which hinders the assessment of trends in transmission underlying the case detection data of countries and control programmes of the 1990s.

Transmission models

Leprosy involves a transmission cycle, like any other infectious disease. Because of this, interventions not only have direct effects but also indirect effects, which are difficult to assess. For instance, chemotherapy not only cures a patient, but also prevents transmission by this patient and by those who would have been infected by this patient if he/she were left untreated. Similarly, BCG vaccination not only prevents leprosy cases due to the protection afforded (direct effect), but also the transmission that the prevented cases might have caused (indirect effect).

Epidemiological transmission models for an infectious disease explicitly describe the transmission process, the course of infection and disease, and the way interventions act. This allows for exploration of both the direct and indirect effects of interventions. By using a transmission model in addition to statistical techniques in analyses of datasets, more knowledge can be gained about the features of a disease that determine the potential impact of interventions, and about the impact of these interventions. The consequences of gaps in knowledge about a disease can be addressed by varying assumptions about uncertain aspects of the disease in so-called sensitivity analyses. Transmission models also enable the prediction of future trends in the transmission and incidence of a disease, and prospective evaluation and comparison of the impact of interventions. Epidemiological transmission models are therefore commonly used. The first models were introduced one century ago to investigate the regular recurrence of measles epidemics and the relationship between numbers of mosquitoes and the incidence of malaria (*53*). Over time, models of varying complexity were developed for a wide range of diseases, for instance including childhood diseases, sexually transmitted diseases, and diseases caused by microparasites or macroparasites whose transmission

cycle involves intermediate hosts. The development of models for tuberculosis, which is like leprosy caused by a mycobacterium, was initiated in the 1960s and still continues (e.g. (*54-60*)). The first model for leprosy was developed in the 1970s by Lechat (*61*).

Group-compartmental models

The SIR-model is the most basic model used for infectious diseases (*53*). It has three compartments: 'susceptible', 'infected' and 'recovered'. In a SIR-model, new-borns are susceptible. Susceptibles can acquire infection due to transmission, and can subsequently recover. The infected group is assumed to be infectious, and recovery is assumed to imply immunity for new infections. Everyone can die. A SIR-model has three state variables which describe the fractions of the total population in each of the compartments. The behaviour of a SIR-model over time is reflected in the changes in its state variables. These changes can be described and analysed mathematically because they are fully determined by four parameters: a birth rate, a transmission parameter which reflects the infectiousness of the compartment 'infected', a recovery rate which specifies how fast recovery from 'infected' takes place, and a death rate which applies to each of the three compartments.

The SIR-model is a so-called group-compartmental model. It can be modified and/or extended to describe specific diseases more realistically. For instance, a higher death rate can be used for the 'infected' compartment to account for the fact that a disease may have fatal consequences. And the 'recovered' compartment can be omitted for diseases for which recovery does not lead to immunity: in this case, recovery leads to a transition back to the 'susceptible' compartment. Most tuberculosis models are group-compartmental models (e.g. (*58, 60*)). A general feature of tuberculosis models is that the 'infected' compartment is split up into several compartments: most tuberculosis infections do not lead to disease, but some will proceed to infectious pulmonary disease or non-infectious disease (pulmonary or extrapulmonary). Similarly, in modelling leprosy, one might distinguish 'PB leprosy' and 'MB leprosy' and account for long incubation periods. Group-compartmental models can be made age specific: a new copy of each compartment can be used for each age group considered. Sex-specificity is another option. Group-compartmental models are often used to explore the impact of interventions. To account for vaccination, one can add a 'vaccinated' compartment. Chemotherapy treatment of infections implies an increase of the recovery rate, and thus a shortening of the duration of the infectious period. The above shows that the complexity of group-compartmental models can be increased step by step. Simulation techniques are used to analyse the behaviour of group-compartmental models when mathematical analysis becomes very complicated or impossible.

Lechat's leprosy models

Inspired by early tuberculosis models, Lechat developed a group-compartmental model for leprosy and refined it later (*61, 62*). The models were used to predict the impact on

the transmission of leprosy of case detection in combination with either dapsone monotherapy or MDT treatment (*63-65*). Both dapsone and MDT were predicted to have an almost immediate impact on the incidence (which refers to onset of disease). With dapsone, the incidence decreased by less than 8% per year. In contrast, the impact of MDT was predicted to be much faster: the decrease in incidence was about 25% per year. The decline in case detection was of the same order of magnitude. Such fast and high declines in annual case detection after the introduction of MDT have not been reported in literature, see also Chapters 2 and 3. The predictions therefore appear to be overoptimistic.

Lechat made a few assumptions which led to the favourable predictions, and which are in conflict with present-day knowledge about leprosy epidemiology. Firstly, an average duration for the incubation period of MB leprosy of 2.2 years was used, which is much shorter than the available data suggest (*4*). This causes the turn-around time of the transmission cycle to be much too short. Secondly, the assumed delay between onset of disease and start of treatment was too short (see e.g. (*66-68*)), which is important because patients starting MDT transmit only during this delay. Thirdly, patients were assumed to remain fully infectious during the first year of dapsone treatment (see (*18*)), which resulted in overestimation of the impact of MDT-based as compared to dapsone-based control.

Lechat also used his models to investigate the impact of hypothetical vaccines ('BCG-like' and other) (*62, 63*). In the simulations, the vaccines were administered at only one point in time, and to entire populations or fractions of them, independent of age. Due to the targeting of all age groups, the vaccination strategies almost immediately had an impact on incidence trends. The simulated vaccination policies differ from those implemented in practice. The policy in most developing countries is to give BCG once in young childhood. The rationale for this is to prevent serious childhood forms of tuberculosis (see section 1.2). Further questions addressed by Lechat include the assessment of the impact of isolation of patients and of improved compliance to dapsone monotherapy on transmission (*63*), of the consequences of the emergence of primary dapsone resistance (*62*), and of the cost-effectiveness of interventions (*64, 69*).

Leprosy epidemiology is fraught with uncertainties, several of which are not taken into account in Lechat's models. Some examples are:

- Does natural immunity occur, and if so, how frequently?
- How long is the incubation period of leprosy?
- Are individuals incubating for leprosy disease already infectious?
- Does most transmission by infectious individuals occur soon after onset of disease?

The framework for modelling leprosy transmission, SIMLEP, that we developed is conceptually quite similar to Lechat's models. However, SIMLEP is more flexible in possibilities for varying assumptions, and a wide range of models can be defined within
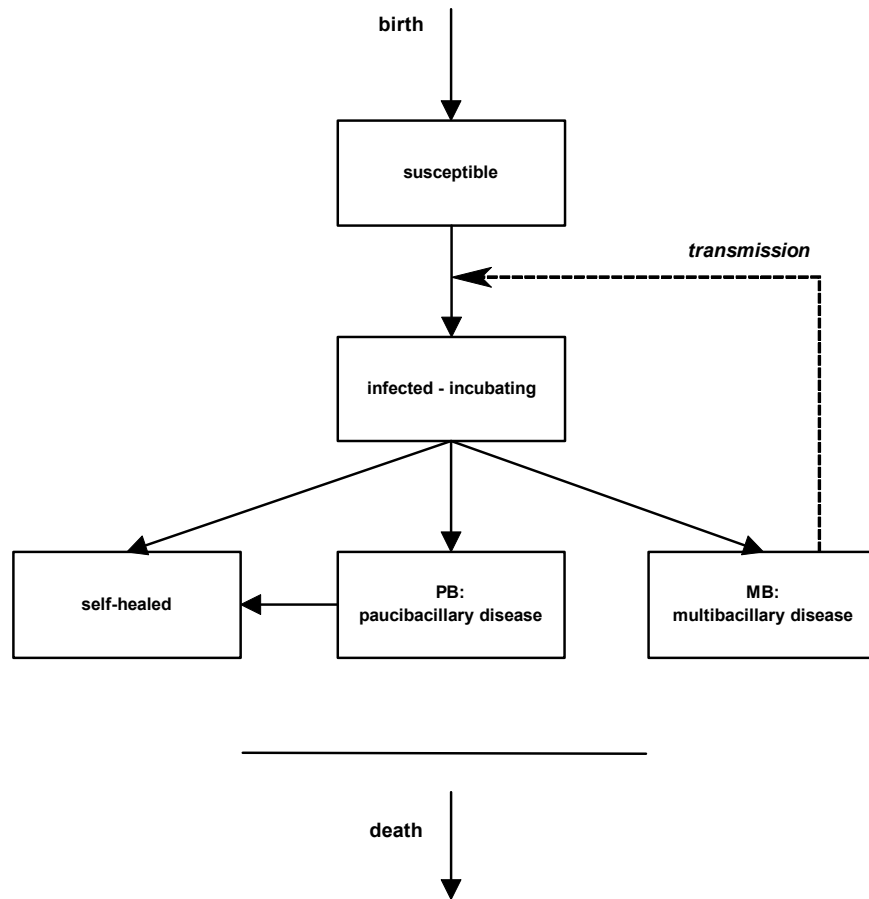
Figure 1.1 Example of a SIMLEP model describing the natural history of leprosy infection and disease. Newborns are susceptible. Susceptibles can become infected due to transmission. New infections either self-heal, or incubate to one of two forms of leprosy disease: infectious disease which does not self-heal ('multibacillary disease'), or non-contagious self-healing disease ('paucibacillary disease'). Everyone can die. The arrows represent birth, death and state changes, and the dashed arrow represents transmission.

SIMLEP including models that can deal with the four questions listed above. Figure 1.1 gives an example of a SIMLEP model in which all transmission is caused by individuals with MB leprosy disease. With the group-compartmental SIMLEP framework, existing longitudinal data can be analysed in order to explore which uncertain aspects of transmission, course of infection and disease determine the impact of control strategies on transmission most. In this thesis, the extensive database on the disappearance of leprosy from Norway between 1850-1920 is employed for this purpose (*70*). The question to what extent the Norwegian policy of isolation of patients – which resembles chemotherapy in terms of preventing transmission – contributed to the decline is also

investigated. Socio-economic improvement is considered as alternative explanation: the decline coincided with continuous growth of the Norwegian economy (*70*). In SIMLEP, strategies of BCG vaccination and chemotherapy-based control – nowadays the only interventions that are implemented at a large scale – can be specified in detail, and can be varied over time. Using the results of the Norway study, the impact of these strategies can be assessed with more scrutiny, and scenario predictions for the future of leprosy can be made.

1.5 Research questions and outline of the thesis

This thesis aims to investigate the impact of present day control activities on the transmission and incidence of leprosy, and on the occurrence of leprosy induced impairment. The specific research questions are:

1. What were the trends in leprosy case detection rates in recent decades?
2. Can these trends be explained, and do they provide evidence for an impact of leprosy control on transmission?
3. To what extent have isolation of patients and socio-economic improvement contributed to the disappearance of leprosy from Norway?
4. Which uncertain aspects of leprosy epidemiology contribute most to the uncertainty about the impact of leprosy control on transmission?
5. What is the impact of present day control – case detection and chemotherapy, BCG vaccination – on the transmission of leprosy?
6. What is the relationship between the delay in case detection and the impairment status of patients at the time of detection, and how does the impairment status change during treatment and after release from treatment?

Chapter 2 systematically reviews published time trends in case detection in leprosy endemic areas and countries from different continents (question 1). The variation in trends within individual areas is investigated using information on leprosy control activities. Special attention is given to the question whether the introduction of MDT has led to changes in case detection trends, and to possible implications for transmission (question 2). On the basis of combined information from various data sources, **Chapter 3** presents trends in case detection and case detection rate (CDR) since 1985 for 14 important endemic countries which together dominate the global case detection figures (question 1); explanation of the trends is problematic due to lack of information on control activities.

Chapter 4 gives a detailed description of the epidemiological transmission modelling framework SIMLEP that we developed to address the questions 3-5. The full set of mathematical equations describing SIMLEP is given in an appendix to Chapter 4.

In **Chapter 5**, SIMLEP is used to analyse the disappearance of leprosy from Norway between 1850 and 1920. Estimates and uncertainty limits for the contributions of the Norwegian policy of isolation of patients versus socio-economic improvement are derived (question 3). The aspects of leprosy epidemiology which are responsible for the uncertainty limits are identified (question 4).

Chapter 6 presents a scenario analysis of trends in the transmission and incidence of leprosy. Uncertain aspects of leprosy epidemiology and BCG vaccination are accounted for. The scenarios assume that dapsone monotherapy is replaced by MDT in 1990. For each scenario, SIMLEP is first fitted to the historical trend in average case detection rate for major endemic countries, and incidence rates are projected up to 2020. Subsequently, the annual decline in the projected incidence rate over 2000-2020, which reflects the decline in transmission, is calculated (question 5).

The relationship between the delay in case detection and the impairment status of patients at the start of treatment with chemotherapy (question 6, first part) is investigated in **Chapter 7**. This is done on the basis of intake data on new leprosy patients enrolled in a long-term prospective study in Ethiopia – the ALERT MDT Field Evaluation Studies, or AMFES – of the consequences of the use of MDT for the individual patient. Follow-up data from the same study are used in **Chapter 8** to assess the impairment status of patients both at release from treatment, and two to four years later (question 6, second part).

In the General Discussion (**Chapter 9**), concise answers are given to the six research questions, and the answers are discussed. In addition, the prospects for reducing the global prevalence of leprosy induced impairment are investigated on the basis of the results of the scenario analysis from Chapter 5 and of the studies on impairment caused by leprosy from Chapters 7 and 8. Finally, conclusions and recommendations are given.

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2

Trends in leprosy case detection rates

2.1 Summary

Background A systematic review of the trends in leprosy incidence is lacking. The question of whether leprosy transmission has declined, remains, therefore, unanswered. This study investigates trends in new case detection rates (NCDRs) in selected leprosy-endemic areas from different continents.

Methods A literature search using specific inclusion criteria was performed. Average annual rates of change in NCDRs were obtained by exponential curve fitting. The variation in trends within individual areas was investigated using direct and indirect information on leprosy control activities.

Results This review covers 16 areas in the Pacific, Asia, Africa and Latin America. For 10 out of the 16 areas, the trend was seen to be declining consistently over the last 10 years or longer. Near stabilization or stabilization after decline was observed for two areas. For three areas, interpretation of recent NCDRs was difficult due to changes in control, but two of them showed a decline over the study period. A consistently increasing trend was observed over the last 20 years in the one remaining area. The observed downward trends could not be attributed to reduced control activities or changed diagnostic criteria. A general acceleration of downward trends in NCDR after the introduction of multidrug therapy (MDT) has not so far occurred.

Conclusion Our main conclusion is that despite many differences between the studies and study areas, the review demonstrates a considerable tendency of downward NCDR trends. Lack of information and changing control conditions necessitate caution in interpreting NCDR trends in individual areas. A general impact of MDT on NCDR trends is so far not visible. The coming years will be crucial for MDT-based control to prove its ability to reduce leprosy incidence.

2.2 Introduction

The prevalence of leprosy, as measured by number of cases registered for treatment, and the new case detection rate (NCDR) are the conventional indicators for monitoring trends in leprosy control and elimination programs.

Dapsone was the only available drug for several decades. In dapsone-based programs, treatment duration was variable, often for 10 years or even lifelong. Registered prevalence would be cumulative figures affected by mortality and migration of patients.

From the early 1980s onward, dapsone has gradually been replaced by the more effective multidrug therapy (MDT). Under MDT, the leprosy elimination goal has been formulated as a reduction in prevalence to a level below 1 per 10,000 population by the year 2000 (*1*). There will only be a direct relationship between registered prevalence and NCDRs when new cases are put on treatment and when the recommended MDT treatment duration does not change over time. Under this condition, trends in registered prevalence and in NCDRs will little differ during the MDT era.

Trends in NCDRs reflect trends in incidence rates provided that no significant changes occur in case detection efforts, self reporting behavior, and diagnostic procedures and criteria. Incidence is here defined as the first appearance of clinically detectable signs which would lead to the diagnosis of "leprosy". The NCDR does not depend on the duration of treatment. Therefore, the NCDR is a better indicator than registered prevalence for monitoring trends in transmission over extended time periods during which both dapsone- and MDT-based programs have been carried out.

Crude worldwide data suggest that the number of newly detected cases has remained roughly constant for 10 years. It stood around 560,000 in 1994 (*2*). The present paper provides an overview of trends in NCDRs for different areas of the world, which were selected on the basis of peer-reviewed publications satisfying quality and completeness criteria. Other information, e.g. on changes in case detection efforts and on the impairment status of newly detected cases, is used in order to assess whether trends in NCDRs indeed reflect trends in incidence. The impact of the main interventions – early detection, chemotherapy treatment and BCG vaccination, which generally has been rationalized as a preventive measure against tuberculosis but which may be equally or more effective against leprosy (*3*) – on NCDR trends is discussed. This discussion includes the possible consequences of MDT introduction on incidence.

2.3 Materials and methods

The publications for this review were selected as follows. A literature search in Medline from 1986 onward was performed. A publication was selected as a candidate for the review when its abstract in Medline made reference to information on new case detection, incidence or the prevalence of leprosy. Candidate publications for which the denominator

of the NCDRs was well defined and for which newly detected cases were representative for the new case load in an area were included in the next selection step. Examples of rejections are publications on new cases which were by majority imported, or on new cases reporting to a hospital in an area where other case detection activities took place. Only publications which presented a series of at least 10 NCDRs over a period including 1986 and covering at least 10 years of continuous case detection, or which contained references pertaining to the same study which present these series, were maintained in the last selection step. The only source used apart from scientific journals is the proceedings of the meeting on "Leprosy profiles with special attention to MDT implementation" (Tokyo: Sasakawa Memorial Health Foundation, 1991).

In order to interpret the observed NCDRs and to assess whether their trends reflect trends in incidence, the selected journal publications and proceedings were scrutinized for information on (changes in) other epidemiological indicators and (changes in) operational aspects of control programs. Relevant information includes population size and density; the profile of newly detected cases (impairment and disability status, single lesion proportion, type index, smear positivity); mean age at detection and age-specific new case detection rates (both by year of detection and by year of birth); prevalence rates at the start and end of the study period; occurrence of relapses; diagnostic criteria and procedures; delay until detection; drug regimens used; organization of control and the continuity of control services over time (e.g., case detection methods, transition from a vertical to a horizontal control program, history of BCG vaccination) and, finally, evidence for socioeconomic development.

Spearman's rank correlation coefficients between calendar year and NCDR were calculated. Exponential curves were fitted to the NCDRs over the period covered by the time series. The explained proportion of the variation in the time series, the R^2 coefficient for the fitted curves, was calculated. R^2 is a measure of goodness of fit of the curve to the data.

2.4 Results

The journal publications and proceedings which were selected cover 16 areas, namely, 7 Asian, 5 African and 3 Latin American areas and French Polynesia (Pacific islands). The number of cases detected, population size and NCDR study period are given in Table 2.1. The prevalence rate and NCDR at the start and at the end of the study period vary widely among the areas under review (Table 2.2). The study period exceeds 25 years for six areas.

The NCDRs for all areas are plotted on a logarithmic scale (Figure 2.1). On visual inspection, a downward trend can be observed for most areas. In areas with monotonous declines, trends are (about) linear on a logarithmic scale. This supports the use of exponential curve fitting of the data (i.e. constant proportional annual changes in the NCDR). Curve fitting confirmed the decline of the NCDR for all areas except Brazil and Guyana, which show small increases in the NCDR (Tables 2.3 and 2.4).

Table 2.1 Areas selected in a literature search for a trend analysis of new case detection rates.

Area	Study period	New cases detected in 1988	Population in millions (1986-1990)	Population density in persons per sq. km. (1986-1990)[h]
Pacific Islands				
French Polynesia	1946-1990	7[a]	0.2	61
Asia				
Wenshan Prefecture (China)	1958-1993	130[b]	2.8	83
Weifang Prefecture (China)	1955-1993	30[b]	8.7	511
Philippines	1955-1990	2,442	59	197
Visakhapatnam District (India)	1977-1993	3,375	3.1	228[i]
Bhutan	1982-1992	73	0.6[f]	13
Thailand (country)	1964-1990	2,200[b]	55	107
Thailand (3 N. provinces)	1976-1990	–[c]	–[c]	–[c]
Africa				
Uele Region (Zaire)	1975-1988	213	1.7	–[c]
Malawi	1977-1993	907	8.2	69
Ethiopia (country)	1975-1988	4,700[b]	46	41
Shoa Region (Ethiopia)	1975-1989	1,100[b]	11	129
Rwanda	1977-1987	44[d]	6.6	251
Latin America				
Brazil	1950-1987	19,685[d]	143	17
Guyana	1975-1987	60[e]	0.8[g]	4
Mexico	1980-1989	284	78	40

[a] Data aggregated into 3-year periods; newly detected cases in 1988-1990 = 21.
[b] NCDR in 1988 x population size for 1986-1990.
[c] Not available.
[d] Newly detected cases in 1987.
[e] NCDR in 1987 x estimated population size for 1990.
[f] Official population size for 1990, 1.4 million, is probably inaccurate (*4*).
[g] Estimated population size for 1990 as by The World Bank. *World Development Report 1993*. New York: Oxford University Press, 1993.
[h] Areas for regions as by publication, for countries as by *The Times Atlas of The World*. London: Times Books, 1995.
[i] Population density for Andhra Pradesh State (Health Monitor. Pune, India: Foundation for Research in Health Systems, 1993) which encorporates Visakhapatnam District.

The five areas with the smallest rates of decline, below 5%, are situated in Asia and the Pacific: French Polynesia, Wenshan Prefecture (China), the country Thailand, The Philippines and Visakhapatnam District, India. The declines for all other areas exceed 8%, with a maximal decline of 19% for the Uele Region in Zaire (Table 2.3).

Table 2.2 New case detection rate (NCDR) and prevalence rate in the 16 areas at the beginning and at the end of the study period.

Area	Study period		NDCR/1000/year		Prevalence rate/1000	
	Years	Length	Start of period	End of period	Start of period	End of period
Pacific Islands						
French Polynesia	46-90	45	0.25	0.04	2.4	0.14
Asia						
Wenshan Prefecture (China)	58-93	36	0.71	0.04	1.4	0.12
Weifang Prefecture (China)	55-93	39	0.29	0.0004	0.27	0.004
Philippines	55-90	36	0.07	0.05	0.41	0.67
Visakhapatnam District (India)	77-93	17	1.1	0.8	2.3	0.8
Bhutan	82-92	11	0.19	0.07	4.2	0.24
Thailand (country)	64-90	27	0.21	0.03	5	0.23
Thailand (3 N. provinces)	76-90	15	0.16	0.06	2.5	0.14
Africa						
Uele Region (Zaire)	75-88	14	2.22	0.12	10.8	0.6
Malawi	77-93	17	0.47	0.06	3.1 [a]	0.16 [b]
Ethiopia (country)	75-88	14	0.33	0.10	2.6 [c]	– [d]
Shoa Region (Ethiopia)	75-89	15	0.28	0.08	1.9	0.33
Rwanda	77-87	11	0.012	0.007	0.26 [e]	0.17
Latin America						
Brazil	50-87	38	0.09	0.13	– [d]	1.8 [f]
Guyana	75-87	13	0.08	0.07	0.9	0.2
Mexico	80-89	10	0.009	0.003	0.23	0.2

[a] Prevalence rate in 1980.
[b] Prevalence rate in 1991.
[c] Average prevalence rate for period 1976-1981.
[d] Not available.
[e] Prevalence rate in 1982.
[f] Prevalence rate in 1989 (*5*).

In concordance with the curve fitting results, all Spearman's rank correlation coefficients are negative, except for Brazil and Guyana (Table 2.3). For the small average annual changes of the NCDR, natural fluctuations are expected to be an important source of variation in the data. It is, therefore, not surprising that Brazil, Guyana, and the areas with lower declines also have smaller Spearman's rank correlation coefficients and R^2 coefficients. The relatively high coefficients of French Polynesia can be explained from

New case detection rate /1000 /year

(a) Pacific and East Asia

Wenshan

Fr. Polynesia

Philippines

Weifang

Calender year

New case detection rate /1000 /year

(b) South Asia

Visakhapatnam District (India)

Bhutan

Thailand

Calender year

New case detection rate /1000 /year

(c) Africa

Uele Region (Zaire)

Shoa Region (Ethiopia)

Malawi

Rwanda

Calender year

New case detection rate /1000 /year

(d) Latin America

Brazil

Guyana

Mexico

Calender year

Figure 2.1 Trend in new case detection rate (NCDR) for 14 of the 16 areas covered by this review. Not given are the three northeastern provinces of Thailand and Ethiopia, which show trends similar to Thailand and the Shoa Region in Ethiopia. Rates from before 1955 were only available for French Polynesia and Brazil. The rates for the period 1991-1993 for Weifang are smaller than 0.001 per 1000 per year. ▼ = introduction of treatment regimens containing rifampin, usually MDT.

Table 2.3 Analysis of new case detection rates: average annual decline of NCDR corresponding to exponential curve fit, Spearman's rank correlation coefficient between calender year and NCDR and R^2 coefficient of exponential curve fit.

Area	Average annual decline	Rank correlation	R^2 coefficient
Pacific Islands			
French Polynesia	3.5%	-0.84	0.77
Asia			
Wenshan Prefecture (China)	4.9%	-0.85	0.67
Weifang Prefecture (China)	13.4%	-0.99	0.93
Philippines	2.0%	-0.44	0.27
Visakhapatnam District (India)	0.9%	-0.26	0.05
Bhutan	9.4%	-0.95	0.91
Thailand (country)	3.8%	-0.60	0.36
Thailand (3 N. provinces)	8.3%	-0.67	0.49
Africa			
Uele Region (Zaire)	19.0%	-0.91	0.77
Malawi	11.2%	-1.00	0.99
Ethiopia (country)	9.7%	-1.00	0.90
Shoa Region (Ethiopia)	8.9%	-0.93	0.90
Rwanda	10.3%	-0.91	0.65
Latin America			
Brazil	-0.7%	0.26	0.08
Guyana	-2.5%	0.23	0.07
Mexico	12.8%	-0.95	0.93

the aggregation of data into 3-year periods, which dampens much of the year-to-year variability.

The individual areas are analyzed in more detail and related to available information on control programs and case detection methods.

Pacific islands

French Polynesia (6, 7). A new leprosy control program was implemented in French Polynesia by the end of the 1940s. The NCDR declined between 1946 and 1967 and remained roughly stable until 1987. Transmission induced by relapses of nearly half of the multibacillary (MB) patients after dapsone monotherapy might have contributed to the stabilization according to Cartel, *et al.* (*6*). The leprosy control program organizes active case finding among household contacts and passive case finding. MDT was introduced in

Table 2.4 Declines in new case detection rates in the 16 study areas.

Average annual decline	No. areas
< 0%	2
0% – 5%	5
8% – 20%	9

1982, resulting in intensified active case finding in household contacts and improved management and follow up of patients. The relapse rate with MDT so far was nil. The NCDR clearly decreased in the last 3-year period, 1988-1990.

Asia

Wenshan Prefecture (China) (*8*). Leprosy control was initiated in the late 1950s as part of the national program. In the first years, much effort was placed on case finding, possibly explaining the higher NCDRs of 1958 and 1959. A downward trend was observed over the period 1962-1993. The two upward peaks of the NCDR coincide with the establishment of a network of eight county skin disease control stations (1973) and the introduction of rifampin in combination with dapsone (1979). The beginning of MDT in 1986 was followed by increased control activities, and no clear decline in the NCDR is visible since.

Weifang Prefecture (China) (*8, 9*). A leprosy control program was initiated in 1955. A consistent decline in NCDRs is observed with some elevations coinciding with so-called clue surveys for Shandong Province to which Weifang belongs. These surveys were carried out in 1955-1958, 1965-1966, 1971-1972, 1975-1976 and 1983-1984. More intensified case finding took place in the 1980s. MDT was introduced in 1986. Only 10, 9, 5, 4 and again 5 new cases were detected in the successive years between 1989 and 1993 in a population of 8.7 million in 1992. These recent cases were mainly self reporting.

The Philippines (*10*). Case finding methods were not explicitly described. Five-year NCDRs were available for 1955-1985, and also annual data for 1987 to 1990. Leprosy control activities were resumed from 1946 onward. Mobile skin clinics were established between 1955 and 1959. Only a small decline of the NCDR was observed over the years 1955-1975, followed by a more rapid decline over the decade 1975-1985. Transition from a vertical control system to an integrated health service approach took almost two decades, but was completed before the start of MDT in 1988. The NCDR has risen sharply during 1986-1989, i.e. just before and during MDT introduction.

Visakhapatnam District (India) ((*11*) and Report on the workshop on impact of MDT on trend of leprosy. Madras: Indian Association of Leprologists, 1994). Data were presented from mid-year to mid-year; Figure 2.1 displays the year 1976-1977 as the calendar year 1977. A significant downward trend is not observed. The early peak in NCDR in 1980

remains unexplained. Both the proportion voluntary reporting cases among total new cases and the NCDR for actively detected cases among the examined population (annual decline 4.5%) showed important fluctuations. General population surveys are the most important component of active case finding. It is also carried out through contact surveys and school surveys. MDT was introduced in 1984-1985.

Bhutan (*4*). A vertical program had already been operational for some years before the establishment of the National Leprosy Control Programme in 1981. MDT was introduced in 1982 and data were presented from 1982 onward. The population of Bhutan had a natural growth rate during the study period, but there was also large scale emigration. The NCDRs were, therefore, based on the same population size for all years. Contact and group surveys continued throughout. Mass surveys were held on a regular basis until 1988 and were subsequently gradually replaced by focal surveys in areas of previously known high prevalence. The proportion self reporting, the proportion with disability, and the proportion with high smear positivity among newly detected cases increased during the study period (*4*). Interpretation of the quite regular downward trend in NCDR is, therefore, in our opinion not straightforward. The MDT coverage was below 10% in 1982 and above 80% from 1988 onward, with a coverage of 89% by the end of 1992.

Thailand (*12, 13*). A specialized program was established in Thailand in 1955, and revision to an integrated program started in 1970. A sharp decline in the NCDR was observed in 1971. The integration was completed in 1977, covering 67 of the 73 provinces of Thailand. The NCDR increased from 1972 onward, peaked in 1981, and declined ever since, with an average annual decline of 10.0% for the period 1979-1990 as compared to 3.8% for the study period as a whole. During the years 1984-1990, MDT gradually replaced dapsone monotherapy. Household contact surveillance, rapid village surveys (mobile clinics), school surveys, and skin clinic services have been practiced regularly throughout, although the degree of intensity of some of these methods varied over time. The three highly endemic northeastern provinces for which the specialized program approach was maintained have a similar trend as Thailand as a whole (*13*).

Africa

Uele Region (Zaire) (*14, 15*). The leprosy control system was interrupted from 1964 to 1974 and was gradually reorganized afterward. Case finding is passive; the control program includes up to 20 mobile teams that contact patients monthly. The NCDR fell sharply in the initial years after 1974, which might be due to a reduction of false-positives in case ascertainment (*14*). An initial backlog in case detection cannot be excluded. For the period 1980-1988, exponential curve fitting gives an average annual decline of 5% as compared to 19% for the study period as a whole. Combined treatment regimens, containing rifampin, have been administered from 1981 onward. Leprosy control activities have been progressively integrated into a structure of primary health care introduced in 1983.

Malawi (*16-18*). Methods of leprosy control work during 1973-1983 have been described by Boerrigter and Ponnighaus (*16*). A mobile service organized patient treatment and passive case finding through periodic leprosy clinics. School surveys covered most pupils at least once during 1974-1983. A review of patients on treatment along with the introduction of MDT in 1983-1984 caused a great reduction in the prevalence rate. As a consequence, the number of staff – and self reporting opportunities according to Boerrigter and Ponnighaus (*17*) – were reduced. Otherwise, detection activities have remained comparable throughout 1973-1993 (*17, 18*). The decline of the NCDR is strikingly regular over the entire study period.

Shoa Region (Ethiopia) (*19*). Case detection was almost exclusively passive. Leprosy clinics were either run in general health services or, if nonexistent, in other settings. The observed average decline for the study period as a whole is largely caused by a drop in the NCDR over the period 1980-1985. MDT was introduced in 1983. The pattern for Ethiopia as a whole (*20*) is similar to that of Shoa Region, but the paper presents less information on control.

Rwanda (*21*). A nongovernmental organization organized leprosy control in cooperation with the authorities from 1964 to 1984. MDT was introduced in 1982. Exponential curve fitting up to 1984 gives an average annual decline of 5.3% as compared to 10.3% for the study period as a whole. The overall average annual decline can, hence, for an important part be attributed to the dip in the years 1985-1986. With respect to this dip, Stes and Malatre stated (*21*): "The steep dip during 1985-6, the years of transition, may be due to diminished control activities while the Service National de Lutte Contra la Lèpre was being set up. The 1987 rise could then be seen as a 'catching-up' manoeuvre of previously undetected cases, and is probably a good sign". This implies that the overall average annual decline should be interpreted with caution. The National Service particularly insists on the integration of leprosy control with primary health care. Case detection in Rwanda is based on voluntary reporting at dispensaries or health services on visits of mobile units. Information campaigns are organized and new patients are invited to bring their children and household contacts for examination.

Latin America

Brazil (*5, 22*). Significant upward or downward trends in NCDRs for the period 1950-1987 were not observed. During 1950-1968, when data registration was poor, policy guidelines were not clear, and personnel training and motivation were deficient, the NCDR declined by 3% per year (*22*). Integration of leprosy control activities into primary health care was started by the end of the 1960s. From 1969 to 1987, control programs were improved by the implementation of technical guidelines, decentralization of case finding and case holding and better logistic facilities. The NCDR increased by 6% per year during the period 1969-1987 (R^2 = 0.92, Spearman's rank correlation = 0.96). Region-wise analysis revealed that the observed increase affected the entire country (*22*).

A combination of dapsone and rifampin was given to all MB cases from 1976 onward; gradual implementation of MDT for all new cases started in 1986.

Guyana (*23*). Case finding methods are not described explicitly. The present Guyana Leprosy Control Programme began in 1971. Multibacillary patients received dapsone, clofazimine and rifampin together from 1978 onward. The NCDR increased in the late 1970s following program expansion on receipt of external budgetary support. It peaked directly after the introduction of MDT in December 1981 and declined afterward. The low NCDRs of the early years and the subsequent increase cause the average annual increase of the NCDR.

Mexico (*24*). Case finding methods have not been described explicitly. The vertical National Leprosy Control Program was started in 1960, and was incorporated into the state health services in 1981. At that time, treatment started to include rifampin and clofazimine in several different combinations. The organization of operations was, in this phase, somewhat irregular. In 1989, the program had a national office with several functions, including supervision. A comprehensive program for leprosy control is carried out in the zone with the highest prevalence. The Mexican NCDR showed a quite regular fall during the study period (1980-1989). A plan for the implementation of MDT was developed in 1989 by the National Leprosy Control Office.

2.5 Discussion

Overall pattern

The data from all three continents and the Pacific Islands show a downward trend in the NCDR for most areas considered. The magnitude of the decline does not seem to depend on the population size, population density or leprosy endemicity level - the latter apparently also being independent of population size and population density - of the area (Tables 2.1, 2.2 and 2.3).

Marked differences can be observed in rate of decline between areas and also within areas over the study period. For most areas, including all African areas, this rate exceeds 8%. The rate of decline is below 5% in 4 out of the 5 areas in Asia and the Pacific Islands with study periods longer than 25 years (Tables 2.2 and 2.3). Clearly, it was difficult to achieve a sustained decline over long time periods in these areas. Publication bias can also not be excluded in the sense that time series over longer periods are more prone to be published, whereas short-term trends might only be published in case of success, i.e., clearly declining trends.

Passive and active case detection

NCDR decline did not depend on case detection methods, but it was more variable in areas were case detection involved active components (e.g. household contact surveys, school surveys and general population surveys). Active case finding was often used in

Asia and the Pacific Islands. Passive case finding was generally most important in the African areas.

Departures from overall trend

In some areas, like Uele Region (Zaire) and Wenshan Prefecture (China), sharp initial declines in the NCDR were observed. This might be an artifact caused by detection of many "old" prevalent cases during the first years of leprosy control programs. Only later, newly detected cases will be mostly cases having contracted leprosy recently. If the first years are disregarded, most areas show declines that continue over the full study period or at least over the last decade.

A less favorable picture emerges in three areas where the NCDR remained constant during long periods (French Polynesia, Wenshan Prefecture, Visakhapatnam District) and in two areas with no evidence of a consistent trend during the study period (The Philippines and Guyana). Relapses in French Polynesia were already mentioned. In Wenshan, control activities were increased after the implementation of MDT. A steady pattern over the study period is observed in Visakhapatnam. In Guyana, the NCDR increased following program expansion on receipt of external budget support, and peaked directly after the introduction of MDT. Intensified case finding must have caused the exceptional rise in NCDR just before and during MDT introduction in The Philippines. Clear peaks in new case detection at MDT introduction also have also been reported from, e.g., Madagascar (2). For Visakhapatnam, the absence of a clear peak in the NCDR at MDT introduction can be explained by a phased introduction of MDT.

A distinctly different picture is observed in Brazil: its NCDR increased throughout the entire country during 1969-1987. Considering the clear increase in trends in Brazil and its individual regions and because a lower rate of NCDR increase was observed for lepromatous plus borderline cases than for tuberculoid cases, Motta and Zuniga suggest that the increase in NCDR is not only the consequence of improved awareness by health units, but also reflects a real increase in incidence (22). The Brazilian Coordinator for Sanitary and Dermatology comments that the main operational changes that influence the data did happen after 1986, and supports the suggestion that epidemiological factors contribute to the increase in the NCDR in Brazil up to 1987 (Maria Leida de Oliveira, personal communication). We are not aware of consistently increasing trends in the NCDR in other areas.

Operational factors and declining trends

Operational factors might have been responsible for declines in the NCDR. Reductions in case detection efforts are of particular concern. Reductions have not been reported explicitly, although detection methods changed in Bhutan (replacement of mass surveys by focal surveys). Integration of leprosy control activities into the general health services might also lead to a reduction in case detection efforts. The NCDR was already falling at the time of integration in the Uele Region and in Rwanda. The transition period toward

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integration (1970-1977) coincides with reduced NCDRs in Thailand: the reduction was, however, temporary. Reductions in health personnel in the leprosy program did not coincide with the sharp declines in NCDR in Malawi (*17*).

An increase of impairments and disabilities in an existing control program deserves attention since it might suggest late diagnosis and, hence, reduced control activities. Information on this aspect was incomplete. A definite (but slight) increase in the impairment and disability status of new patients in areas with persistingly declining trends was only seen in Bhutan. The proportion with a high smear positivity among newly detected cases in Bhutan also increased (*4*). Insufficient information prohibited an analysis of the proportion single lesion cases among newly detected cases, which is an indicator for the share of active case detection efforts.

Indicator for declining incidence: increasing age at detection

In Thailand, the mean age at detection increased by nearly 7 years over the last 15 years of the study period while new case detection decreased. Age shifts under declining endemicity were observed in Nigeria, Japan, Venezuela (*25*), Portugal (*26*), Norway (*27*) and Shandong province in China (*9*). The age shift occurred under varying levels of NCDR and could already be discerned after 10 years of declining incidence in, e.g., Nigeria and Japan. The age shifts in Thailand, Norway and Shandong province were of the same order.

Study of trends in age-specific detection rates is more informative. In Thailand, detection rates declined in all age groups between 1976-1980 and 1986-1990. The highest detection rates were observed for age groups older than 35 throughout 1976-1990. During this period, the maximum case detection level first occurred in the age group 45-54 and, in later years, in the age group 55-64. Declining rates for onset of disease for all age groups together with an increasing relative risk for the oldest as compared to the youngest age group were, over time, observed in Portugal (*26*), Norway (*27*) and Shandong Province (*9*). Interestingly, increases in age at onset were not observed over time for these three areas when rates were analyzed by year of birth. Details by year of birth were not available for Thailand.

A shift to detection at older ages combined with increased disability might point to longer delays in detection. However, in Thailand the proportion of patients with impairments and disability did not show a clear increase. This suggests that the age shift in detection is not the consequence of longer delays in detection alone and, thus, reflects a real age shift in incidence. For the other areas with persistently declining trends, information on the age at detection was either not available, or of limited usefulness because of only a short time-period or small numbers involved, or not representative because of increasing proportions of children being examined.

Type index among new cases

The type index (proportion lepromatous or MB among newly detected cases) has been advocated as an indicator for changing trends in leprosy incidence [Report on the group discussions on the needs and prospects for epidemiological tools in leprosy control. WHO workshop on epidemiology of leprosy in relation to control. *Lepr Rev* 1992; 63 (Suppl): 114s-122s.]. This index is, however, sensitive for classification criteria and case detection efforts. Reduced case detection efforts can lead to an increase in the type index because of both self cure and downgrading of tuberculoid (or paucibacillary) cases. An increasing type index during intensification of control has also been observed (Wenshan Prefecture after MDT implementation). In addition, long term declines of leprosy have been observed together with both an increasing and a decreasing type index (*25, 26*). In the present review, the behavior of the type index among newly detected cases also showed much variation, which could not easily be explained.

Variation between studies

The reviewed studies differ in many aspects. Examples are: terminology used, level of detail of available information, length of study periods, leprosy endemicity levels and applied case detection methods, and control strategies over time. NCDRs from the studies were, therefore, analyzed separately with respect to control conditions and underlying trends. One should be careful in directly comparing the trend statistics (Table 2.3) of the areas.

Do trends in the NCDR reflect trends in underlying incidence?

According to the 1988 WHO Expert Committee definition, a case of leprosy is defined as a person showing clinical signs of leprosy, with or without bacteriological confirmation of the diagnosis, and requiring chemotherapy (*28*). Clinical diagnosis is commonly based on the three cardinal signs of leprosy: anesthetic skin lesion(s), enlarged peripheral nerve(s) and the presence of *Mycobacterium leprae* in slit-skin smears or in nasal mucus scrapings (*29*). Diagnosis is not always straightforward. The establishment of loss of sensation in skin lesions can, for example, be difficult. Changes in diagnostic criteria and procedures, in the quality of these procedures, and in case detection efforts (including alertness for leprosy) affect NCDRs. Larger proportions of new cases with very early leprosy having single lesions, with questionable diagnostic specificity and a tendency toward self-healing, can be expected in the case of active case detection when surveys are undertaken at shorter intervals (*30*). Changes in certain administrative and managerial decisions, such as targets for case detection and incentives for MDT activities, are also expected to influence NCDRs (*11*). The above considerations indicate that trends in NCDRs not necessarily reflect trends in underlying incidence. Although evidence was hardly available in the reviewed papers, changes that might prohibit extrapolation of trends in NCDRs to trends in incidence cannot be excluded. Information on the occurrence of relapses and possible inclusion of relapses in NCDRs is also sparse in the reviewed papers.

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Selection of papers

A possible publication bias in the sense of a tendency to publish on high-quality control programs covering long periods of time or indicating successful leprosy control was already mentioned, and cannot be excluded in a review of this type.

The inclusion criteria aimed at selecting papers which report on data that have been collected regularly over time in specific areas. Less refined data are available for large geographical regions and although they should be interpreted cautiously, they are definitely important (*2*). Between 1993 and 1994, new case detection rates for WHO Regions as a whole decreased by 4.5% and 7.8% for, respectively, the Americas and South-East Asia, and increased by 20.8%, 25.9% and 3.3% for, respectively, Africa, the Eastern Mediterranean and the Western Pacific. A reduced NCDR in India explains much of the South-East Asian decrease. Considerable improvement in case detection as a consequence of setting the leprosy elimination target is reported for the African and Eastern Mediterranean Regions. Worldwide leprosy detection has remained about constant over the period 1985-1995 (*2*).

Interaction with tuberculosis

Exposure to other mycobacteria and the risk for leprosy are probably associated. It has, in particular, been argued that *M. tuberculosis* protects against *M. leprae* (*31*). In the Leprosy Prevention Trial (Tamil Nadu, India), however, tuberculin positivity only had very limited influence on susceptibility for leprosy (M. D. Gupte, unpublished data from LPT). A study of a possible correlation between trends in leprosy and tuberculosis calls for a thorough analysis of the appropriate additional information on tuberculosis incidence - tuberculin surveys might be more informative than tuberculosis NCDRs - and on the continuity of data collection activities and tuberculosis control activities.

Role of socioeconomic development

It is generally believed that leprosy incidence declines with improving socioeconomic standards (*32*). The NCDR was already below 1:100,000 in 1985 in Weifang and a further decline in Weifang was steep in the period 1985-1993 while there was no clear decline in Wenshan. During the same period, the economic development is said to have been somewhat slow in Wenshan, whereas Weifang experienced rapid growth (*8*). The gross prefectural product per capita showed a highly significant negative correlation with both the prevalence rate and the NCDR over the period 1985-1991 in both Weifang and Wenshan Prefecture. The correlation of these rates with average annual income over this period is also negative for Weifang, but positive for Wenshan. The latter finding is "... likely due to the increased control activities in Wenshan since the implementation of MDT in 1986 ..." (*8*). Examples of declines in the incidence rate coinciding with rapid socioeconomic development from the literature are: Japan (excluding Okinawa), Okinawa itself (although later) and Taiwan (*33*). Okinawa Prefecture had the slowest rate of economic development in Japan (*34*).

Role of BCG vaccination

BCG vaccination has been shown to provide protection against leprosy. Protective efficacies from 20% to 80% have been reported (*3*). Hence, BCG is expected to prevent new leprosy infections and, subsequently, new sources of infection. BCG vaccination was mentioned for 8 out of the 16 areas in this analysis. Details on vaccination programs are, however, not given and assessment of their impact is therefore not possible. Referring to detection being generally low in children and high in adults, with low detection in indeterminate leprosy, BCG is argued to have played some role in leprosy morbidity reduction in Weifang Prefecture (*8*). This might, however, be questioned because the proportion of ages 0-14 among new cases had been declining in the successive 5-year periods between 1955-1959 and 1975-1979 in Shandong province (incorporating Weifang Prefecture) (*9*); whereas Shandong initiated BCG vaccination only in the 1970s.

Role of chemotherapy

Chemotherapy is thought to have played a role of its own in several areas. Becx-Bleumink identifies dapsone monotherapy as the most probable reason for the decline in Ethiopia (*19*). The motivation is that BCG coverage of newborns was less than 25% in the 1980s and probably not higher in the 1970s and earlier; whereas, in addition, improvement in the socioeconomic conditions of the rural Ethiopian population during the last decades would at most have been very marginal. A second example is the possible role of chemotherapy control in the initial decline of the NCDR (1946-1966) in French Polynesia where economic development really only started after 1962, and where systematic BCG vaccination was introduced by the mid-1960s (*6*).

The impact of chemotherapy is generally difficult to assess because socioeconomic development, BCG vaccination, and control through chemotherapy often go hand in hand. MDT is at present, however, regarded as the mainstay for leprosy control by WHO (*1*). The rationale for this WHO policy is clear. Early diagnosis and effective treatment do not only cure individual patients, but may significantly reduce leprosy transmission. This requires a drug regimen that is easily accepted by leprosy patients, such as MDT, which became available in the 1980s. The advantages of MDT include the absence of treatment failures due to drug resistance, very low relapse rates following completion of treatment, fixed and relatively short duration of treatment, and very low frequency of side-effects (*1*). MDT improves patient compliance, encourages early self reporting, motivates health workers, and can induce a considerable upgrading of leprosy control activities (*35*).

Dapsone monotherapy renders patients noninfectious within a reasonable short period of time but lacks the favorable indirect effects of MDT. An acceleration of declining trends in NCDRs after MDT introduction might, therefore, largely be attributed to these indirect effects of MDT. The combined use of its main bactericidal drug, rifampin, with other drugs preceded the introduction of MDT in some areas. Accelerations of declining trends after the introduction of these combined regimens or MDT can be observed only in the country of Thailand and in Weifang Prefecture, where case finding intensified in the

1980s and where the NCDR was already very low at MDT introduction in 1986 (Figure 2.1). In French Polynesia, where the NCDR had stabilized, the NCDR dropped in the last 3-year period, 5 years after MDT introduction.

Skepticism on the possible impact of chemotherapy exists, and the literature provides some examples. A stabilization of NCDRs which could not be attributed to operational factors was observed in the dapsone-based programs of two Leprosy Control Units of the Gandhi Memorial Leprosy Foundation (Sevagram, T. Narsipur) (In retrospect & prospect. Wardha: Gandhi Memorial Leprosy Foundation, 1974). A controlled attempt to assess the impact of drug therapy (rifampin) on incidence failed to show any effect after 5 years in Myanmar (*31*). Another finding relates to tuberculosis: similar declines in tuberculosis prevalence were reported from a special intervention (with chemotherapy) area and the "control" area were no special treatment facilities had been introduced (*36*).

Various explanations can be given for the absence of accelerations under MDT. The incubation period of leprosy is not well known but usually believed to be several years, implying that it might still be too early to see pronounced accelerations. Reductions in transmission might also be masked by increased case detection efforts as part of MDT implementation policies (e.g. The Philippines). It is also possible that not yet detected cases are responsible for transmission. This might imply that detection is too late to reduce transmission much, possibly even to the extent of prohibiting an impact of leprosy chemotherapy on transmission. A related observation is an average period between the patient's first observation of signs of leprosy and diagnosis of 2.3 years in Ethiopia (July 1987 - July 1989) (*19*). The delay until detection in Wenshan Prefecture was between 2 and 5 years for 24% and longer than 5 years for 8.2% of newly detected cases (period 1986-1993) (*8*).

WHO is also studying the relationship between incidence and new case detection (*2*). Preliminary results of collaborative studies indicate that the majority of cases are detected late, even in programs that have used MDT for many years: "... in the majority of countries, only a small proportion of newly detected cases (10%) are true incident cases; about 75% of newly detected cases started 3-5 years earlier and about 15% are detected 5 to 10 years after the onset of the disease." The gap between the estimated number of cases and those actually registered for treatment is said to be very large in some countries (Bangladesh, Indonesia, Viet Nam, Mali, Niger and Sudan). Big gaps between estimated and registered prevalence were also noticed in places in India, where sample surveys were undertaken or where intensive case detection campaigns were carried out even after 4 years of MDT implementation. A study in six subcenters, however, revealed a large proportion of cases detected during surveys to be cases of "early leprosy" (*11*).

Several other mechanisms for transmission have been mentioned. These include subclinically infected persons (*37*), carriers of *M. leprae* in the nose within endemic populations (*37-40*) and animal reservoirs and the presence of *M. leprae* in the soil (*41*). It has been hypothesized that everyone in an endemic population will harbor *M. leprae* at some time, and that clinical leprosy arises from a pool of subclinical infection and not by

transmission from an individual index case (*42*). If some of these factors indeed play a role in transmission, then early detection and chemotherapy treatment of cases might very well be insufficient to have a major impact on leprosy trends. The importance of these factors is, however, not clear and, at present, cannot be established for want of appropriate investigation tools.

Conclusion

Our main conclusion is that despite many differences between the studies and study areas, the review demonstrates a considerable tendency of downward NCDR trends. Lack of information and changing control conditions necessitate caution in interpreting NCDR trends in individual areas. A general impact of MDT on NCDR trends is so far not visible. The coming years will be crucial for MDT-based control to prove its ability to reduce leprosy incidence.

2.6 Acknowledgment

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3

Trends in leprosy case detection worldwide since 1985

3.1 Summary

Trends in case detection and case detection rate (CDR) since 1985 are described at regional and national levels. Annual case detection by WHO Region was available for 1994-2000. Using different sources, complete time series for case detection were constructed for 1985-1998 for a group of 33 endemic countries cumulatively (top 33), and for 14 individual countries (top 14). Population statistics were used to derive CDRs. India contributed 79% to global case detection in 1998. Africa, the Americas and South-East Asia each contributed about 30% when India is excluded. During 1994-2000, case detection did not decrease in these three WHO Regions. The 33 countries contributed 99% and 98% to global case detection in 1994 and 1998, respectively. Cumulative case detection for the top 33 minus India gradually increased, overall almost doubling. The contribution of the top 14 to case detection of the top 33 hardly changed over time, equalling 96% in 1998 (81% when India is excluded). In terms of annual case detection, Brazil was always ranked second after India; it accounted for 27% of 1998 case detection in the top 33 except India. In 1998, seven of the top 14 countries – including India and Brazil – had CDRs above 2 per 10,000. The CDR did not exceed 1 per 10,000 for the other half. Decreasing tendencies in CDR, either for the whole period or in the 1990s, are observed for four of the top 14 countries (Guinea and three Western Pacific countries: China, Vietnam and the Philippines). In conclusion, there is no general decline in case detection to date, and several important countries still have high CDRs. Prevalence is an irrelevant indicator for monitoring epidemiological changes in leprosy. Trends in the transmission and incidence of leprosy are still completely unclear, necessitating further research. The target to eliminate leprosy as a public health problem, defined as a prevalence of less than 1 per 10,000, is therefore also an inadequate yardstick for decision making on leprosy control.

3.2 Introduction

The annual number of leprosy cases detected globally each year has not declined since 1985 (*1, 2*). Yet, in May 2001, it was announced that leprosy was 'eliminated as a public health problem' at a global level. The 44th World Health Assembly (WHA) in 1991 defined the elimination target as a prevalence of less than one patient per 10,000 population (*3*). At a national level, the World Health Organization (WHO) schedules the elimination target to be reached in all countries by the end of 2005 (*4*). The discrepancy between the trend in global case detection and proclaimed and expected elimination at global and national levels requires further explanation.

The target indicator for elimination – prevalence per 10,000 population – is not univocal. Reported prevalence refers to numbers of patients in leprosy registers, and is sensitive for the treatment duration. This follows directly from the simple formula 'number on treatment = case detection × average treatment duration'. The treatment duration became much shorter with the gradual replacement of dapsone monotherapy by multidrug therapy (MDT). In addition, there was no consistency in register keeping: following the introduction of MDT, many (ex-)patients not in need of treatment, but possibly with complications or disabilities due to leprosy, were removed from existing registers (*5, 6*). In fact, the 1991 WHA resolution did not state the exact meaning of prevalence; the definition of the seventh WHO Expert Committee on Leprosy only includes patients registered for chemotherapy (*7*). In any case, the reported prevalence figure fell dramatically, from over five million in 1985 to 750,000 in the year 2000, due to the shortening of the treatment duration and the change in register keeping. The achievement of the elimination target is based almost solely on these two factors, because global case detection did not decrease.

Leprosy control has achieved a great deal since the introduction of MDT, mainly because millions of patients have been bacteriologically cured. However, WHO's strict emphasis on the elimination target (as defined above) has been criticized (*6*). Successful leprosy control should bring about reductions in transmission and incidence (i.e. onset of disease), leading to true reductions in case detection. Previously, we conducted a literature review of published trends in leprosy case detection rates (CDRs) up to 1993 (*8*). In this review, the CDR was declining in most areas/countries, as opposed to the global trend since 1985. We could not demonstrate that the observed declines were due to leprosy control, and pointed out the possibility of publication bias in the sense of a tendency to publish on high-quality programs covering long periods of time or indicating successful control.

Since the review, additional information has become available which allows for the construction of a time series of case detection at various levels of geographical aggregation. This information includes case detection data at country level from 1985 onwards for 14 countries which together account for 94% of global case detection in

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1998. This paper gives a description of trends in case detection and CDR since 1985. By doing so, we aim to improve the understanding of the global leprosy trend and the present day situation at regional and national levels, looking beyond the currently defined target to eliminate leprosy as a public health problem as the sole yardstick of success of leprosy control.

3.3 Material and methods

Data on case detection in five WHO Regions during 1994-2000 (Africa, Americas, Eastern Mediterranean, South-East Asia and Western Pacific) are taken from a 2002 issue of *Weekly Epidemiological Record* (*2*). The number of cases detected annually in the sixth WHO Region, Europe, is negligible compared to case detection in these five regions (in 1998, less than 100 new cases were reported in Europe (*9*)). Therefore, 'global' case detection during 1994-2000 is calculated by summing the case detection figures for the first five WHO Regions.

Cumulative data on case detection for the 'top 32 endemic countries' during 1985-1998 are taken from two issues of *Weekly Epidemiological Record* (*1, 10*). The first issue reported that these countries provided consistent information over the last 13 years, and that they represented '93% of the current global leprosy burden and 85% of that of 1985' (*10*). The exact meaning of this phrasing is unclear. Due to insufficient data, we could not extend the time series of cumulative case detection for the top 32 to the years 1999 and 2000. We extended the top 32 to a 'top 33' by adding case detection data for China for 1985-1998 (see below). In alphabetical order, the 32 countries are Bangladesh, Benin, Brazil, Burkina Faso, Cambodia, Chad, Colombia, Congo, Democratic Republic of the Congo, Côte d'Ivoire, Egypt, Ethiopia, Guinea, India, Indonesia, Madagascar, Mali, Mexico, Mozambique, Myanmar, Nepal, Niger, Nigeria, Pakistan, Philippines, Senegal, Sudan, Thailand, Venezuela, Viet Nam, Yemen and Zambia.

For 13 countries of the top 32 and China, complete case detection time series could be constructed for the period 1985-1998 using two sources of information. The first is a document prepared for the International Conference on the Elimination of Leprosy that was held in New Delhi, India in October 1996 (*11*). This report provides annual case detection figures for 1985-1995 for a large number of leprosy endemic countries. To extend the time series, the data are supplemented with national figures on case detection for the years 1996-1998 as reported by countries to WHO. WHO has provided these figures in subsequent issues of *Weekly Epidemiological Record* (*1, 9, 12, 13*). Using an additional issue (*14*), the resulting time series could be extended with case detection data for the years 1999 and 2000 for the majority of these 14 countries (top 14). For other countries, we briefly summarize information on 1998 case detection (*9*). In alphabetical order, the 14 countries are Bangladesh, Brazil, China, Ethiopia, Guinea, India, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Philippines, Sudan and Vietnam.

Time series of mid-year population sizes of individual countries required to calculate CDRs are obtained from the World Bank's 2002 World Development Indicators CD ROM (*15*). Time series for the mid-year size of the world population for the years 1994-2000 are based on data from the U.S. Bureau of the Census (*16*).

The appendix to this paper provides the full time series of case detection and CDR of individual countries, combinations of countries, WHO Regions and the world that are the subject of this paper.

3.4 Results

WHO Regions

Table 3.1 and Figure 3.1 give details on global case detection with distribution by WHO Region for the period 1994-2000. Just over 800,000 cases were detected globally in 1998, with South-East Asia accounting for 86% of the new caseload. India alone contributed almost 80% (Table 3.2), and Africa, the Americas and South-East Asia minus India each about 30% when the Indian figures are excluded. The contributions to case detection in 1994-2000 as a whole are of the same order as for the year 1998. Decreasing tendencies in case detection are not observed in Africa, the Americas and South-East Asia. Case detection decreased in the last 3 years in the Western Pacific. A clear pattern is not observed in the remaining Eastern Mediterranean region.

Top 33 endemic countries

Table 3.2 and Figure 3.2 provide the cumulative case detection data for the top 33 endemic countries for the period 1985-1998. The 33 countries contributed 99% to the global case detection and 96% to the global detection when India is excluded in 1994, and

Table 3.1 Case detection by WHO Region, 1994-2000.

WHO Region	Population in millions 1998	Cases detected 1994	Cases detected 1998	Cases detected 2000	Case detection ratio: 2000 over 1994 corrected[a]: no	Case detection ratio: 2000 over 1994 corrected[a]: yes	Percentage of global case detection (1998, %) including India	Percentage of global case detection (1998, %) excluding India
Africa	619	47,900	51,530	54,602	1.1	1.0	6%	30%
Americas	802	36,623	47,218	44,786	1.2	1.1	6%	28%
Eastern Mediterr.	453	6504	5923	5565	0.9	0.7	1%	3%
South-East Asia	1480	456,882	689,069	606,703	1.3	1.2	86%	32%
Western Pacific	1639	12,737	10,617	7563	0.6	0.6	1%	6%
World	5905	560,646	804,357	719,219	1.3	1.2	100%	—

[a] Corrected for population growth (no/yes).
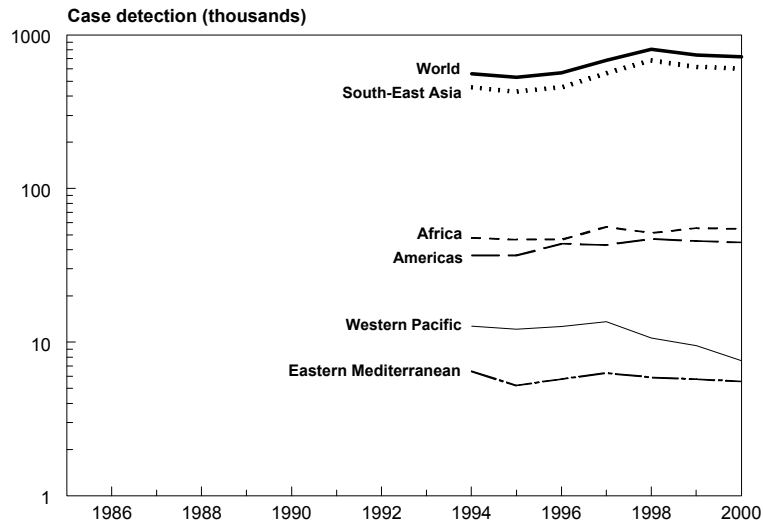
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Case detection (thousands)

Figure 3.1 Global case detection and detection by WHO Region, 1994-2000.

98% and 91% in 1998. We could not derive these percentages for earlier years. The cumulative CDR of the 33 countries was rather stable during 1985-1998. However, a gradual increase in cumulative CDR results after excluding India, which heavily dominates the cumulative case detection data (Figure 3.2). The annual number of new cases detected in the top 33 minus India about doubled between 1985 and 1998 (Table 3.2).

The CDR level is also relevant: throughout 1985-1998, the Indian CDR is much higher than the CDR of the top 33 minus India (12 times higher in 1998). However, China is included in the top 33 minus India. It has a huge population but does not contribute much to total case detection. By consequence, the deviation from the Indian CDR decreases from 12 to a factor 6.5 when China is also excluded (Table 3.2). This indicates that the level of the CDR of combinations of countries should be interpreted with caution. This also holds for the global CDR which exceeded 1 per 10,000 per year during 1997-2000: contributing 98% to global case detection, the top 33 countries constituted only 64% of the 1998 world population. For similar reasons, we refrained from calculating CDRs for the WHO Regions.

Top 14 countries

The contribution of the 14 countries for which case detection time series could be constructed to the total case detection in the top 33 countries hardly changed during 1985-1998. In 1998, this contribution was 96%, and 81% when India is excluded (Table 3.2). Similarly, the contributions to the global case detection in 1998 were 94% and 73%. The trend in cumulative case detection of the top 14 almost parallels the trend in

Table 3.2 Case detection and case detection rate (CDR) for each of the top 14 countries, for the top 14 and top 33 endemic countries combined with and without India and China included, and global case detection and CDR, 1985-1998.

Area	Population in millions	Cases detected		CDR /10,000/year		Ratio: 1998 over 1985		Contribution to case detection in top 33 except India (%)	
	1998	1985	1998	1985	1998	Cases	CDR	1985	1998
Africa									
Ethiopia	61	5113	4457	1.18	0.73	0.9	0.6	6.5%	2.9%
Guinea	7	200	3684	0.40	5.20	18.4	13.0	0.3%	2.4%
Madagascar	15	2016	8957	1.99	6.14	4.4	3.1	2.6%	5.8%
Mozambique	17	955	3764	0.71	2.22	3.9	3.1	1.2%	2.5%
Americas									
Brazil	166	19,265	42,055	1.42	2.53	2.2	1.8	24.6%	27.4%
Eastern Mediterranean									
Sudan	30	77	2077	0.03	0.69	27.0	20.2	0.1%	1.4%
South-East Asia									
Bangladesh	127	4834	12,351	0.50	0.98	2.6	2.0	6.2%	8.0%
India	980	477,000	634,901	6.23	6.48	1.3	1.0	—	—
Indonesia	204	8313	18,367	0.51	0.90	2.2	1.8	10.6%	12.0%
Myanmar	47	6600	14,357	1.78	3.08	2.2	1.7	8.4%	9.4%
Nepal	22	4999	6570	3.09	2.99	1.3	1.0	6.4%	4.3%
Western Pacific									
China	1242	4964	2051	0.05	0.02	0.4	0.3	6.3%	1.3%
Philippines	73	1139	3490	0.21	0.48	3.1	2.3	1.5%	2.3%
Vietnam	77	2062	2162	0.35	0.28	1.0	0.8	2.6%	1.4%
Country combinations									
Top 14 except China, India	844	55,573	122,291	0.85	1.45	2.2	1.7	71.1%	79.7%
Top 14 except India	2086	60,537	124,342	0.35	0.60	2.1	1.7	77.4%	81.0%
Top 14	3066	537,537	759,243	2.17	2.48	1.4	1.1	—	—
Top 33 except China, India	1534	73,224	151,411	0.63	0.99	2.1	1.6	—	—
Top 33 except India	2777	78,188	153,462	0.35	0.55	2.0	1.6	100.0%	100.0%
Top 33	3756	555,188	788,363	1.86	2.10	1.4	1.1	—	—
World	5904	—	804,357	—	1.36	—	—	—	—

India, due to the numerical dominance of India. For the top 14 except India, cumulative new case detection increased between 1987 and 1992, and further increased between 1995
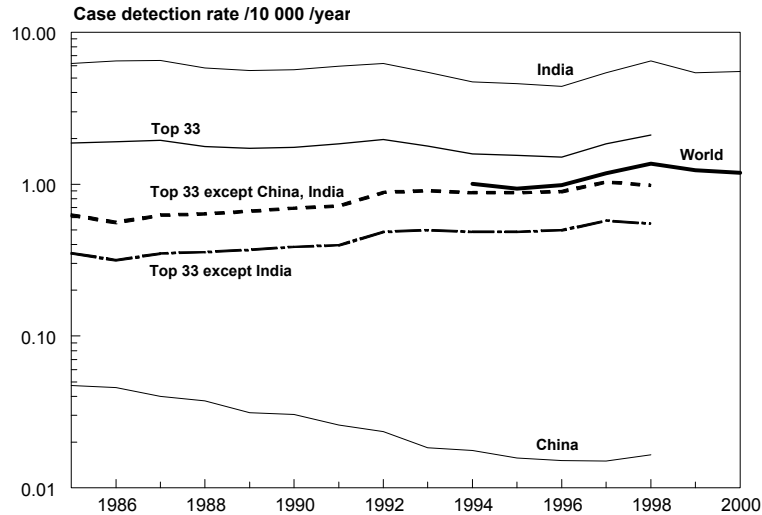
Case detection rate /10 000 /year

Figure 3.2 Case detection rate for India, China, and the top 33 endemic countries with and without India and China included, and the global case detection rate, 1985-2000.

and 1998, with a ratio of 1998 to 1985 case detection of 2:1.

Africa The four African countries of the top 14 contributed 40% to the total 1998 case detection in the region (Tables 3.1, 3.2). The 1998 CDR was above 5 per 10,000 for two countries (Guinea, Madagascar) and above 2 per 10,000 for a third (Mozambique). Over time, the CDR about tripled in Madagascar and Mozambique, with even larger increases in new case detection due to population growth (Table 3.2, Figure 3.3). The Ethiopian CDR initially decreased, but was stable in the 1990s. After an initial increase, the Guinean CDR shows a decreasing tendency from 1992 onwards, although it again peaked in 1997.

Americas Brazil is ranked second after India in terms of country-wise annual case detection. In 1998, it accounted for 25% of global case detection except India (top 33: 27%), and for 89% of case detection in the Americas. The annual Brazilian CDR gradually increased during 1985-1998, exceeding 2 per 10,000 from 1992 onwards. Additional information shows that the increase started around 1970 (*8*).

Eastern Mediterranean In 1998, Sudan accounted for 35% of case detection in the region. Reported detection increased strongly between 1985-1989 (annually: less than 100 cases) and 1994 when it peaked (3070 cases), and fluctuated between 2000 and 2700 new cases per year afterwards. The annual CDR was always below 1 per 10,000, except for the year 1994.

South-East Asia In 1998, India contributed 79% to global case detection (top 33: 81%),

Case detection rate /10 000 /year

(a) Africa and Eastern Mediterranean

Case detection rate /10 000 /year

(b) Western Pacific and Americas

Case detection rate /10 000 /year
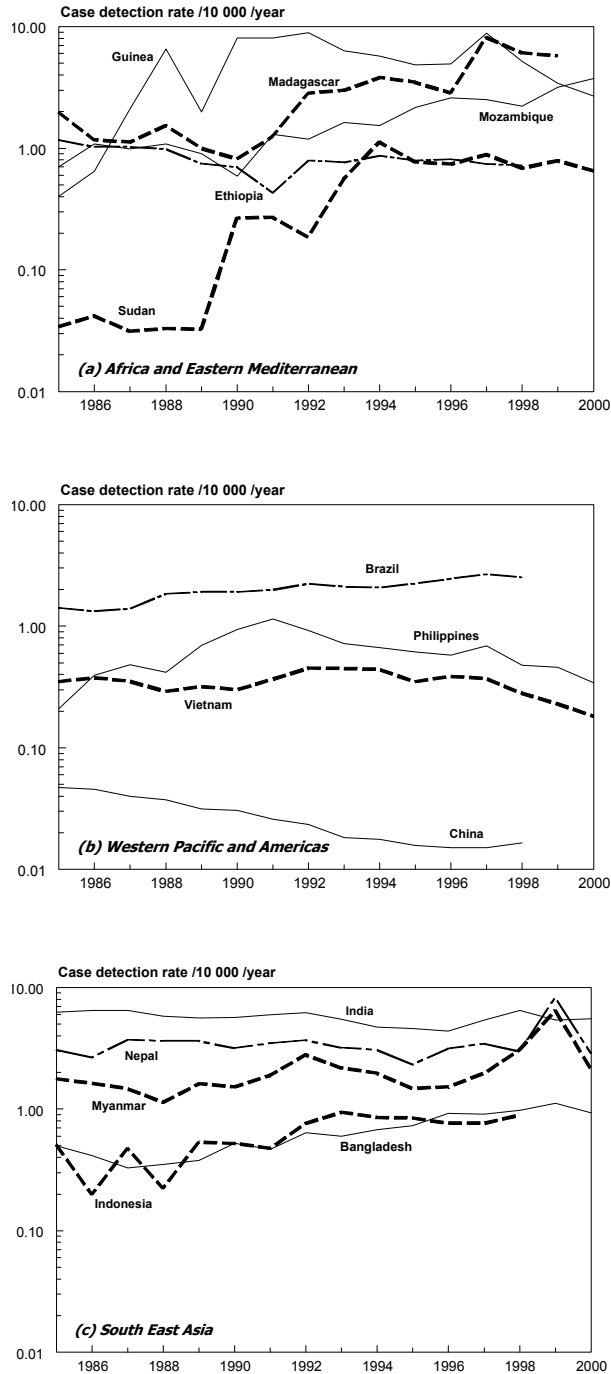
(c) South East Asia

Figure 3.3 Case detection rates for each of the top 14 endemic countries, 1985-2000.

and 92% to detection in the region. The Indian CDR decreased by 2.7% per year between 1985 and 1996 (exponential curve fit; half-value time 25 years), and subsequently increased. The CDR always exceeded 5 per 10,000, except for 1994-1996. The Indian population increased by about 30% between 1985 and 2000. By result, cumulative case detection during 1997-2000 was higher than in any of the three other four-year periods (case detection = CDR × population size).

Bangladesh, Indonesia, Myanmar and Nepal each detected more than 6000 cases in 1998, and together accounted for 30% of 1998 global case detection except India (top 33: 34%), and for 95% of case detection in South-East Asia except India. Overall, the CDRs did not decrease in the four countries. The country with the largest population, Indonesia, detected most cases in 1998, but also had the lowest CDR. It never exceeded 1 per 10,000 per year. In Bangladesh, the annual CDR gradually increased, equalling about 1 per 10,000 in the late 1990s. Case detection tripled, comparing 1997-2000 with 1985-1988. In Myanmar, the annual CDR always exceeded 1 per 10,000, and increased. The Nepali CDR was also always above 1 per 10,000 per year: a clear trend is not visible. The CDR peaked in 1999 in both Myanmar and Nepal, with values that were more than twice as high as those for both 1998 and 2000 (1999 CDRs: 6.5 and 8.3 per 10,000, respectively).

Western Pacific In 1998, China, the Philippines and Vietnam contributed only 5% to global case detection except India (top 33: also 5%), and 73% to detection in the region. Annual CDRs were always below 1 per 10,000, except for the Philippines in 1991. The CDR attained its highest values in the early 1990s in the Philippines and Vietnam, and decreased thereafter. The Chinese CDR gradually decreased from 4.7 per 100,000 in 1985 to 1.6 in 1995, and was stable during 1995-1998. Additional information shows that the Chinese CDR has been on the decrease during the last 4 decades (*17*).

Additional information for the year 1998 (*9*)

Africa Four countries accounted for an additional 30% of African case detection in 1998, each also detecting at least 2500 cases (Democratic Republic of Congo, Niger, Nigeria and Tanzania). After Madagascar, most cases were detected in Nigeria (7230 cases, 14% of African detection, CDR /10,000/yr: 0.6). Overall, twelve African countries had a 1998 CDR of more than one per 10,000 (Angola, Benin, Cameroon, Central African Republic, Congo, Côte d'Ivoire, Guinea, Madagascar, Mali, Mozambique, Niger, Tanzania).

Americas All American countries except Brazil detected fewer than 1000 patients in 1998, and had CDRs below 1 per 10,000.

Eastern Mediterranean Three countries accounted for an additional 60% of 1998 case detection in the region (Egypt, Pakistan and Yemen). Only Egypt detected more than 1000 cases. The CDR was below 1 per 10,000 for all countries in the region.

South-East Asia In 1998, both Thailand and Sri Lanka detected in between 1000 and 1500 cases. Their CDRs were below 1 per 10,000 per year. Information for other countries was not available, indicating prevalences of less than 100 registered cases (*9*).

Western Pacific With 1609 cases, Cambodia accounted for another 15% of 1998 case detection in the region. Its 1998 CDR was 1.45 per 10,000. All other countries reported less than 500 new cases. Still, three of these other countries also had 1998 CDRs of 1 per 10,000 or more (Federated States of Micronesia, Papua New Guinea and Marshall Islands; the latter country had a 1998 CDR of over 20 per 10,000).

3.5 Discussion

This paper uses leprosy case detection data that are based on country statistics and aggregated information from WHO. Figures may sometimes be incomplete or involve inaccuracies due to difficulties in many countries in the collection, processing and reporting of data. Overdiagnosis and reregistration of previously treated cases may also have influenced the detection figures (*9*). Nevertheless, the presented case detection data are the best available and do allow for crude analyses comparing countries and regions. We have analysed these data at three levels: number of cases detected, level of the case detection rate (CDR), and trend in CDR and case detection. Time series for other indicators which may help to assess trends in leprosy transmission, in particular child proportion in new case detection, mean age at detection and age-specific case detection rates (*18*), could not be constructed and detailed information on how control programmes evolved over time is not available.

Number of cases detected

Case detection figures indicate the number of patients that health services need to treat, and provide information on the geographical distribution of new cases in the world. Throughout 1985-1998, by far most cases were detected in India (on average 490,000 cases per year, 79% of global detection in 1998). Brazil always ranked second after India. With an average of 31,000 cases per year, it dominated case detection in the Americas. South-East Asia, which includes India, accounted for 86% of the 1998 global case detection of about 800,000 cases. The WHO Regions Africa, the Americas and South-East Asia each contributed about 30% to the 1998 detection of 170,000 cases, which remains after India is excluded. Virtually all other cases are detected in the Eastern Mediterranean Region and the Western Pacific; detection in Europe is negligible compared to the other regions. Excluding India, 73% of global case detection in 1998 (124,000 cases) is concentrated in the other 13 countries of the top 14 in this study.

Case detection rate (CDR)

The CDR is a crude indicator for comparisons between countries of the relative severity of leprosy as a public health problem. In 1998, half of the top 14 countries had CDRs above 2 per 10,000 (Table 3.2). The CDR did not exceed 1 per 10,000 for the other half. India, the country that dominates global case detection, also had the highest CDR in 1998. For an additional four Western Pacific and 12 African countries, the CDR was also above 1 per 10,000.

CDR levels for combinations of countries should be interpreted with caution. Table 3.2 shows that these levels strongly depend on whether certain countries, in particular India (many cases, huge population) and China (relatively few cases, huge population), are included in the calculations or not. Also in India itself, leprosy is not distributed evenly: according to recent figures, 70% of its new case detection is concentrated in five out of the 25 Indian states (*1*). Concerning the global CDR, it should be realized that 36% of the world population does not live in leprosy endemic countries, and that China contributes less than 1% to present global case detection, but another 20% to the world population. Therefore, we do not consider the *level* of the global CDR to be informative for combinations of countries. We did not calculate CDRs at the level of WHO Regions.

Trend in case detection rate (CDR) and case detection

Trends in CDRs reflect trends in incidence rates, provided that no significant changes occur in case detection efforts, self reporting behaviour, or diagnostic procedures and criteria. The sources of information from which we derived the time trends in case detection and CDR do not provide information on control programmes of countries and changes in them. However, it can be stated that the adoption of the elimination resolution by the World Health Assembly in 1991 led to intensification of leprosy control in many countries (*19*). Geographical coverages of control programmes improved, and many countries initiated Leprosy Elimination Campaigns (LECs) in the late 1990s. In view of this, it is not surprising that the 1998 CDR was lower than the 1985 CDR for only three countries of the top 14 (Table 3.2: China, Ethiopia and Vietnam). Decreasing tendencies in CDR, either for the whole period or in the 1990s, are only observed for four countries (Figure 3.3: Guinea and the three Western Pacific countries: China, Vietnam and the Philippines). Further findings are that the case detection figures for the three WHO Regions with most cases, Africa, the Americas and South-East Asia, increased between 1994 and 2000 (Figure 3.1), and that the cumulative CDR for the top 33 except India gradually increased between 1985 and 1998, overall almost doubling (Figure 3.2). The Indian CDR very slowly decreased up to 1996 and subsequently increased. These observations lead to the overall conclusion that so far, there is no general decline in case detection. Underlying trends in incidence and transmission of leprosy remain completely unclear.

The CDR is more informative than case detection for comparing time trends by country, because the CDR also indicates endemicity levels. It should however be realized that in growing populations, annual case detection may increase substantially with time when the CDR is stable. This follows directly from the simple formula 'case detection = CDR × population size'. During 1985-1998, all top 14 endemic countries experienced population growth, with growth rates ranging from 1.3% and 2.9% per year. By consequence, case detection would have increased by 18% to 45% under constant CDRs during this period. The effect of population growth is also illustrated by the Indian figures in Table 3.2: case detection increased by about 30%, but the CDR hardly changed.

Finally, the time series for the global CDR from 1994 onwards illustrates that the global target for 'elimination of leprosy as a public health problem' has no epidemiological significance: the elimination target would already have been attained by the end of 1994 if all patients had received MDT treatment according to the current guidelines (*7*), and registers had been confined only to those on treatment. This follows directly from the global CDR and the percentage MB in case detection in 1994 (1.01 per 10,000 and 35% of all cases (*2, 10, 16*)) in combination with the formula 'number on treatment = case detection × average treatment duration'. With half a year of MDT treatment for the 65% PB patients and 1 year for the 35% MB patients, the 'on-treatment prevalence' equals 0.65 × 1.01 × 0.5 + 0.35 × 1.01 × 1 = 0.68 per 10,000, which is well below the elimination target of 1 per 10,000. This calculation illustrates that the elimination target, proclaimed to be reached in 2001, was indeed achieved by rigorous implementation of treatment guidelines. Any changes in the epidemiological situation of leprosy are not reflected in this target indicator.

Conclusion

The main conclusion is that to date, there is no general decline in case detection. Several countries with many new cases, including India, still have CDRs exceeding 2 per 10,000 per year. Endemicity levels for combinations of countries should not be summarized in one cumulative indicator, such as the overall CDR. Prevalence is an irrelevant indicator for monitoring epidemiological changes in leprosy. Trends in the transmission and incidence of leprosy are still completely unclear, necessitating further research. The target to eliminate leprosy as a public health problem, defined as a prevalence of less than 1 per 10,000, is therefore also an inadequate yardstick for decision making on leprosy control.

3.6 Acknowledgement

3.7 References

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Appendix: Table 3.A1 Case detection and case detection rate (CDR) for each of the top 14 countries, for the top 14 and top 33 endemic countries combined, and global case detection and CDR, 1985-2000.

Area								Cases detected								
								CDR								
	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
Countries [a]																
Bangladesh	4834	4118	3349	3676	4057	5748	5229	7307	6943	7983	8782	11,225	11,320	12,351	14,336	12,135
	0.5	0.4	0.3	0.4	0.4	0.5	0.5	0.6	0.6	0.7	0.7	0.9	0.9	1.0	1.1	0.9
Brazil [b]	19,265	18,412	19,685	26,482	27,837	28,482	30,094	34,451	32,988	32,785	35,922	39,792	43,933	42,055	–	–
	1.4	1.3	1.4	1.9	1.9	1.9	2.0	2.3	2.1	2.1	2.3	2.5	2.7	2.5	–	–
China	4964	4877	4326	4124	3510	3467	2981	2737	2160	2109	1895	1845	1854	2051	–	–
	0.05	0.05	0.04	0.04	0.03	0.03	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.02	–	–
Ethiopia	5113	4589	4753	4723	3714	3606	2290	4349	4090	4790	4513	4747	4444	4457	–	4931
	1.2	1.0	1.0	1.0	0.8	0.7	0.4	0.8	0.8	0.9	0.8	0.8	0.7	0.7	–	0.8
Guinea	200	330	1110	3542	1115	4652	4788	5434	3968	3668	3194	3326	6117	3684	2475	1986
	0.4	0.6	2.1	6.5	2.0	8.1	8.1	8.9	6.3	5.7	4.8	4.9	8.8	5.2	3.4	2.7
India [c]	477,000	507,000	519,000	474,000	466,000	481,000	517,000	547,000	490,000	429,000	425,571	415,302	519,952	634,901	537,956	559,938
	6.2	6.5	6.5	5.8	5.6	5.7	6.0	6.2	5.5	4.7	4.6	4.4	5.4	6.5	5.4	5.5
Indonesia	8313	3307	8077	3835	9362	9348	8691	14,219	17,693	16,288	16,477	15,071	15,337	18,367	–	13,539
	0.5	0.2	0.5	0.2	0.5	0.5	0.5	0.8	0.9	0.9	0.8	0.8	0.8	0.9	–	0.6
Madagascar	2016	1226	1206	1704	1135	960	1493	3476	3770	4952	4676	3921	11,555	8957	8704	–
	2.0	1.2	1.1	1.5	1.0	0.8	1.3	2.9	3.0	3.8	3.5	2.9	8.2	6.1	5.8	–
Mozambique	955	1483	1373	1508	1269	835	1878	1748	2449	2379	3429	4225	4195	3764	5488	6617
	0.7	1.1	1.0	1.1	0.9	0.6	1.3	1.2	1.6	1.5	2.2	2.6	2.5	2.2	3.2	3.7
Myanmar	6600	6191	5725	4472	6496	6204	7812	11,814	9397	8664	6577	6935	9086	14,357	30,479	10,262
	1.8	1.6	1.5	1.1	1.6	1.5	1.9	2.8	2.2	2.0	1.5	1.5	2.0	3.1	6.5	2.1
Nepal	4999	4434	6300	6305	6470	5780	6515	7032	6287	6170	4783	6602	7446	6570	18,693	6661
	3.1	2.7	3.7	3.6	3.7	3.2	3.5	3.7	3.2	3.1	2.3	3.2	3.5	3.0	8.3	2.9
Philippines	1139	2185	2748	2442	4163	5725	7169	5896	4697	4450	4202	4051	4942	3490	3390	2596
	0.2	0.4	0.5	0.4	0.7	0.9	1.1	0.9	0.7	0.7	0.6	0.6	0.7	0.5	0.5	0.3

Appendix: Table 3.A1 (continued).

	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
Sudan	77	97	74	79	79	661	687	484	1489	3070	2175	2126	2633	2077	2426	2045
	0.03	0.04	0.03	0.03	0.03	0.3	0.3	0.2	0.6	1.1	0.8	0.7	0.9	0.7	0.8	0.7
Vietnam	2062	2292	2183	1847	2075	1995	2500	3142	3185	3173	2566	2883	2808	2162	1795	1446
	0.4	0.4	0.4	0.3	0.3	0.3	0.4	0.5	0.5	0.4	0.4	0.4	0.4	0.3	0.2	0.2
Country combinations [d]																
Top 14 excluding China, India	55,573	48,664	56,583	60,615	67,772	73,996	79,146	99,352	96,956	98,372	97,296	104,904	123,816	122,291	–	–
	0.8	0.7	0.8	0.9	0.9	1.0	1.1	1.3	1.3	1.3	1.2	1.3	1.5	1.4	–	–
Top 14 excluding India	60,537	53,541	60,909	64,739	71,282	77,463	82,127	102,089	99,116	100,481	99,191	106,749	125,670	124,342	–	–
	0.4	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.6	0.6	–	–
Top 14	537,537	560,541	579,909	538,739	537,282	558,463	599,127	649,089	589,116	529,481	524,762	522,051	645,622	759,243	–	–
	2.2	2.2	2.3	2.1	2.0	2.1	2.2	2.3	2.1	1.8	1.8	1.8	2.1	2.5	–	–
Top 33 excluding China, India	73,224	66,790	76,145	79,597	84,743	90,792	96,016	120,133	125,830	124,768	126,845	132,270	156,367	151,411	–	–
	0.6	0.6	0.6	0.6	0.7	0.7	0.7	0.9	0.9	0.9	0.9	0.9	1.0	1.0	–	–
Top 33 excluding India	78,188	71,667	80,471	83,721	88,253	94,259	98,997	122,870	127,990	126,877	128,740	134,115	158,221	153,462	–	–
	0.4	0.3	0.3	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.6	0.6	–	–
Top 33	555,188	578,667	599,471	557,721	554,253	575,259	615,997	669,870	617,990	555,877	554,311	549,417	678,173	788,363	–	–
	1.9	1.9	1.9	1.8	1.7	1.8	1.8	2.0	1.8	1.6	1.5	1.5	1.8	2.1	–	–
World	–	–	–	–	–	–	–	–	–	560,646	529,376	566,567	684,961	804,357	738,112	719,219
	–	–	–	–	–	–	–	–	–	1.0	0.9	1.0	1.2	1.4	1.2	1.2

[a] Case detection figures for 1985-1995 were taken from reference (*11*) in the main text, and figures for 1996,...2000 from (*12,13,9,1,14*), respectively. Mid-year population sizes to calculate CDRs were obtained from (*15*).

[b] Figures for Brazilian case detection in 1997 and 1998 were taken from references (*9*) and (*1*) in the main text, respectively.

[c] The figure for Indian case detection in 2000 was taken from reference (*2*) in the main text.

[d] Case detection figures for the top 14 were obtained by summing the country figures. Case detection figures for the top 33 were obtained by adding the figures for China to the cumulative figures for the top 32, which were obtained from references (*1,10*) in the main text. Global case detection figures were obtained by summing the figures for the WHO Regions Africa, Americas, Eastern Mediterranean, South-East Asia and Western Pacific, which were obtained from (*2*). Mid-year population sizes to calculate CDRs for the top 14 and the top 33 were obtained by summing the country figures, which were obtained from (*15*). Mid-year sizes of the world population were obtained from (*16*). For more information, see main text.

4

SIMLEP:
a simulation model for
leprosy transmission and control

4.1 Summary

SIMLEP is a computer program for modeling the transmission and control of leprosy which can be used to project epidemiologic trends over time, producing output on indicators such as prevalence, incidence and case detection rates of leprosy. In SIMLEP, health states have been defined that represent immunologic conditions and stages of leprosy infection and disease. Three types of interventions are incorporated: vaccination, case detection and chemotherapy treatment. Uncertainties about leprosy have led to a flexible design in which the user chooses which of many aspects should be included in the model. These aspects include natural immunity, asymptomatic infection, type distribution of new cases, delay between onset of disease and start of chemotherapy, and mechanisms for leprosy transmission. An example run illustrates input and output of the program. The output produced by SIMLEP can be readily compared with observed data, which allows for validation studies. The support that SIMLEP can give to health policy research and actual decision making will depend upon the extent of validation that has been achieved. SIMLEP can be used to improve the understanding of observed leprosy trends, for example, in relation to early detection campaigns and the use of multidrug therapy, by exploring which combinations of assumptions can explain these trends. In addition, SIMLEP allows for scenario analyses, in which the effects of control strategies combining different interventions can be simulated and evaluated.

4.2 Introduction

Estimates of the short- and long-term effects of leprosy control strategies are required for decision making, for target setting, and for prediction of the moments at which targets are likely to be reached. However, limited knowledge of leprosy epidemiology and of the effects of population-based interventions make it difficult to explain observed trends in leprosy incidence and morbidity and to predict the future of leprosy.

There is ample evidence that socioeconomic development might affect leprosy transmission, and that secular trends can occur (*1, 2*). BCG vaccination has a protective effect, but its efficacy is highly variable (*3*). The introduction of multidrug therapy (MDT) in the 1980s, with its relatively short duration of treatment, resulted worldwide in rapid declines in the prevalence as defined by the number of cases registered for treatment, and MDT has become the mainstay for leprosy control (*4*). However, convincing evidence for a persistent favorable effect of MDT on new case detection rates has so far not been observed (*5, 6*) and, therefore, the long-term impact of MDT-based programs is not clear.

In this situation, simulation models can help to organize knowledge and assumptions on leprosy and to structure discussions on its control. These types of models enable exploration of the behavior of a disease in populations over time under specified assumptions about processes involved (*7*). The present paper introduces an epidemiological simulation model for leprosy, SIMLEP, which provides a framework for the quantitative description of the dynamics of leprosy transmission, the course of infection and disease, and the impact of interventions. Simulation results on trends in case detection rates and in the prevalence of cases registered for treatment can be compared with observed data. SIMLEP can be used to explore the possible effects of interventions such as MDT-based control on leprosy transmission under assumptions or scenarios on unknown aspects of leprosy epidemiology which can be varied by the user.

In the 1970s and 1980s, Lechat, *et al.* were the first to develop a comprehensive model for leprosy (*8-12*). Their simulations concentrated on the comparison of the long-term impact of alternative control strategies, and helped considerably to clarify the thinking about leprosy control. SIMLEP builds on the approach which is followed in the Lechat model and in several conceptually similar tuberculosis models (e.g. (*13-17*)). Shortly after the introduction of MDT-based control, Lechat, *et al.* made a courageous attempt to explore its consequences (*10, 11*). However, their predicted rapid and persisting decline in incidence has not been observed in reality. In its conclusions and recommendations, the *1991 International Meeting on Epidemiology of Leprosy in Relation to Control* recognized a need for making predictions for future trends, and recommended that simulation models should be developed (*18*). This has initiated the development of the present SIMLEP model. SIMLEP allows for variation of many model assumptions, for example, with respect to natural immunity, the incubation period and asymptomatic infection. Delays for becoming aware of disease and for start of treatment are incorporated, and SIMLEP

also provides different mechanisms for describing leprosy transmission. SIMLEP includes detailed output facilities for comparison of simulation results with observed trends, and for the prediction of future trends.

This paper describes the structure of the SIMLEP model, gives an example of a SIMLEP simulation experiment, and discusses quantification of the model, potential applications and known limitations. Background information on simulation modeling for tropical diseases, and for leprosy in particular, can be found elsewhere (*7, 12, 19, 20*). The Appendix gives a mathematical description of SIMLEP.

4.3 The model

The SIMLEP model describes the process of leprosy transmission, disease and control in a population which is followed over time. SIMLEP has a pre-defined structure of compartments (representing health conditions with respect to leprosy) and flows between compartments (Figure 4.1). Within this framework, the SIMLEP user can specify assumptions about demography, leprosy and interventions by giving birth and death rates and numerical specifications for the flows between the compartments. The arrows with solid shafts and points in Figure 4.1 represent birth, death and the flows (transitions) between the compartments (boxes in the flowchart). The dashed arrows with open heads – or influence arrows – and the "force of infection circle" represent leprosy transmission. The arrows with solid shafts and spearheads indicate flows related to the SIMLEP interventions: vaccination, case detection and chemotherapy. By not using boxes – 0% flows – the user can simplify the model actually used. SIMLEP performs all calculations for each age separately, and represents the epidemiological situation at the end of a simulation time step by the age-specific distribution of the population over the various compartments. The maximum value for the time step in SIMLEP simulations is two months. Flows from compartments are calculated according to (Markov) transition rates if not indicated otherwise. A flow between two compartments, say k and l, is indicated by f_{kl} (both k and l run from a to j, Figure 4.1). The three flows f_{0a}, f_{0b} and f_{0c} represent births, and death from a compartment, say m, is denoted by f_{mz} (m runs from a to j).

Background situation

The history of leprosy control influences future trends of leprosy in an area and is, therefore, simulated in SIMLEP. SIMLEP runs always start from a stable situation, i.e. an age-specific distribution of the population over the various compartments in which no changes over time occur, with all control measures switched off. This stable situation is derived from the numerical specifications for the model parameters and from a user-specified background incidence rate for the first years of interest for the simulation run (incidence being defined as the first appearance of any specific signs or symptoms of leprosy). SIMLEP will automatically fit this background incidence rate at the start of a simulation experiment by tuning the transmission parameter β (is defined later).
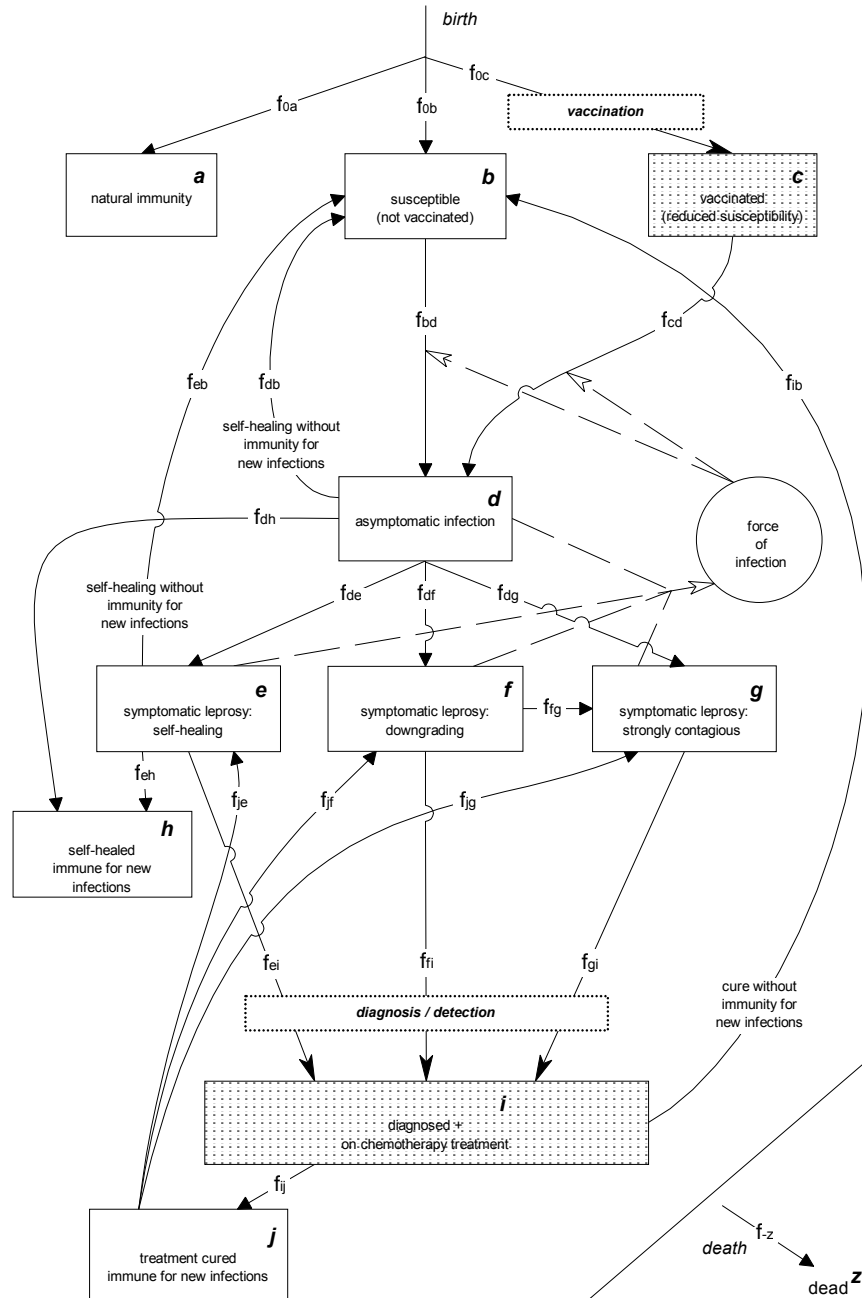
birth

f_{0a} f_{0b} f_{0c}

vaccination

a
natural immunity

b
susceptible
(not vaccinated)

c
vaccinated
(reduced susceptibility)

f_{bd} f_{cd} f_{ib}

f_{eb} f_{db}

self-healing without
immunity for
new infections

d
asymptomatic infection

f_{dh}

force
of
infection

self-healing without
immunity for
new infections

f_{de} f_{df} f_{dg}

e
symptomatic leprosy:
self-healing

f
symptomatic leprosy:
downgrading

f_{fg}

g
symptomatic leprosy:
strongly contagious

f_{eh} f_{je} f_{jf} f_{jg}

h
self-healed
immune for new
infections

f_{ei} f_{fi} f_{gi}

diagnosis / detection

cure without
immunity for
new infections

i
diagnosed +
on chemotherapy treatment

f_{ij}

j
treatment cured
immune for new infections

death f_{-z}

dead **z**

Figure 4.1 SIMLEP: The health states (compartments), the flows between them (arrows), the process of leprosy transmission (dashed arrows and "force of infection" circle) and two interventions: vaccination and diagnosis plus chemotherapy ("intervention" flows and shaded compartments). All transitions are age-specific and the age structure of all compartments is updated at the end of each simulation time step.

Demography

Birth is simulated according to a crude birth rate. A life table governs death in SIMLEP: at the end of each time step, age-specific death rates which correspond to the life table are applied (flows $f_{az}, f_{bz}, .., f_{jz}$) and the age structure of the population is updated. SIMLEP does not consider migration and possible excess mortality in leprosy patients, and does not distinguish between males and females.

Susceptibles and nonsusceptibles

In order to evaluate the potential impact of natural immunity against leprosy, SIMLEP has the option to specify a fraction of newborns to enter the compartment of life-long *NATURAL IMMUNITY* (flow f_{0a}). The other newborns all enter the compartment *SUSCEPTIBLE* (flow f_{0b}). The compartment *SUSCEPTIBLE* can also contain individuals who were cured after treatment without acquiring immunity against new leprosy infections. Upon acquiring a leprosy infection, people from the *SUSCEPTIBLE* compartment move to the compartment *ASYMPTOMATIC INFECTION* (flow f_{bd}).

Course of infection and disease

In SIMLEP, infected individuals are assumed to pass first through an episode without manifestation of specific signs or symptoms of leprosy, which is represented by the compartment *ASYMPTOMATIC INFECTION*. The user can specify time distributions for the length of this episode (see the Appendix). SIMLEP offers the possibility of spontaneous healing of asymptomatic infections without manifestation of symptomatic leprosy (flows f_{db} and f_{dh}). Flows f_{de}, f_{df} and f_{dg} denote the first appearance of any sign or symptom of leprosy (e.g. skin lesion or nerve function impairment) irrespective of recognition by the patient or diagnosis by a medical worker. SIMLEP distinguishes three expression types of symptomatic leprosy:

1. symptomatic leprosy from which all individuals will self-heal when left untreated (via a self-healing rate; flows f_{eb} and f_{eh}): *SELF-HEALING SYMPTOMATIC LEPROSY*;

2. symptomatic leprosy that is not strongly contagious, but from which individuals will downgrade to strongly contagious symptomatic leprosy at a later stage when left untreated (via a downgrading rate; flow f_{fg}): *DOWNGRADING SYMPTOMATIC LEPROSY*; and

3. symptomatic leprosy that is strongly contagious directly upon manifestation of the first signs or symptoms of leprosy: *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY*.

Note that preventing downgrading will enhance the impact of early detection and chemotherapy on transmission. For evidence of downgrading see Scott, *et al.* (*21*). After self-healing from asymptomatic infection or symptomatic leprosy, people either are susceptible for a new infection and move to *SUSCEPTIBLE* (flows f_{db} and f_{eb}), or become immune and move to *SELF-HEALED & IMMUNE FOR NEW INFECTIONS* (flows f_{dh} and f_{eh}).

Possible endogenous reactivation of leprosy in self-healed individuals is neglected. People with symptomatic leprosy move to the compartment *DIAGNOSED + ON CHEMOTHERAPY TREATMENT* as soon as they are detected and are put on treatment.

Transmission

New infections (flows f_{bd} and f_{cd}) are assumed to be caused by contagious individuals in the population. Knowledge on who are responsible for leprosy transmission, and to what extent, is limited. It cannot be excluded, for example, that most transmission occurs in the episode of asymptomatic infection. In SIMLEP, contagiousness is therefore modeled in a flexible way: it can be switched on and off separately for:

1. each of the four groups in compartment *ASYMPTOMATIC INFECTION*, namely, the ones who self-heal without becoming symptomatic, and the people later becoming symptomatic of, respectively, the self-healing, downgrading and strongly contagious types
2. people in compartment *SELF-HEALING SYMPTOMATIC LEPROSY*
3. people in compartment downgrading symptomatic leprosy.

A person with *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY* is assumed always to be contagious, but he might rapidly infect people living close to him. After some time, this person will therefore have transmitted *Mycobacterium leprae* to most of his susceptible contacts. To account for this, the capability to transmit *M. leprae* gradually decreases over time (it follows a negative exponential function) for all persons who enter the compartment *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY*. This loss of contagiousness can be quantified by the average contagiousness – c_{loss} – of all people in the compartment *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY* relative to the level of contagiousness at entry in this compartment.

For the compartments for which contagiousness is optional (*ASYMPTOMATIC INFECTION*, *SELF-HEALING SYMPTOMATIC LEPROSY*, *DOWNGRADING SYMPTOMATIC LEPROSY*), the user should specify a second (lower) level of contagiousness relative to the initial level in the compartment *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY*. Because of this lower level, SIMLEP does not postulate loss of contagiousness for the compartments *SELF-HEALING SYMPTOMATIC LEPROSY* and *DOWNGRADING SYMPTOMATIC LEPROSY*. Presently, the symplifying assumption has been made that the duration of the episode of asymptomatic infection is following the same time distribution for those who self-heal without development of symptoms and those who proceed to symptomatic leprosy of either the self-healing or the downgrading type. A different time distribution can be specified for those who proceed to *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY*. The contagiousness in compartment *ASYMPTOMATIC INFECTION* is assumed to build up gradually to the level of strong contagiousness for those who move to *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY*, and to the second (lower) level of contagiousness for those who do not.

SIMLEP translates the (weighted) contagiousness of all contagious people together into the force of infection (circle in Figure 4.1) which is the rate at which individuals who are still susceptible acquire *M. leprae* infection (flow f_{bd}). For example, if only people in the compartment *DOWNGRADING SYMPTOMATIC LEPROSY* are contagious in addition to the people from the compartment *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY*, then the force of infection *FOI* is equal to

$$FOI = \frac{\left(w_{weak} \; \beta \; F \; + \; c_{loss} \; \beta \; G \right)}{N}$$

with c_{loss} as in above text and

β = measure for contagiousness of people who just entered the compartment *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY*

w_{weak} = weighting factor: the level of contagiousness in the compartments *SELF-HEALING SYMPTOMATIC LEPROSY* and *DOWNGRADING SYMPTOMATIC LEPROSY* is given by $w_{weak} \cdot \beta$

F = number of people in the compartment *DOWNGRADING SYMPTOMATIC LEPROSY*

G = number of people in the compartment *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY*

N = total population size.

The fraction among the susceptible people that acquires *M. leprae* infection during a simulation time step (Δt) is calculated from this force of infection and equals $FOI \cdot \Delta t$. If other compartments are also (weakly) contagious, the people in these compartments are added to the *FOI* term. The gradual buildup of contagiousness in the compartment *ASYMPTOMATIC INFECTION* is described in more detail in the Appendix. Secular declines in leprosy can be taken into account by an annual reduction factor for the transmission parameter β.

Leprosy control

Vaccination

BCG vaccination is often given in early childhood. It only offers protection to a certain degree (*3*). In SIMLEP, vaccination is assumed to take place at birth with a user-defined coverage. Vaccinated newborns without natural immunity enter the compartment *VACCINATED (REDUCED SUSCEPTIBILITY)* (flow f_{oc}). People in this compartment can still be infected but at a lower rate (flow f_{cd}). In a study in South India, the protective efficacy of BCG for younger ages decreased from 58% to 18% over a period of 15 years (*22*). The protective efficacy can therefore be specified to depend on the time since vaccination.

Diagnosis

Early case detection reduces the delay between onset of symptomatic leprosy and start of chemotherapy. In SIMLEP, this delay consists of two consecutive parts: cases must first become aware of their disease ("awareness delay"), before they can look for care after a certain "reporting delay". The user specifies case detection by choosing two rates which are associated with the awareness delay and the reporting delay, respectively. A reporting delay which is infinitely long corresponds with absence of treatment.

Chemotherapy

Chemotherapy shortens the average duration of contagiousness of patients. It is believed that with rifampin bacterial kill is achieved almost instantaneously at the first dose, and that dapsone monotherapy can achieve this effect in about 3 months. However, for simplification, both dapsone monotherapy and multidrug therapy are in SIMLEP assumed to start at the moment of diagnosis and to immediately stop the contagiousness of patients.

Upon starting treatment, patients move to the noncontagious compartment *DIAGNOSED + ON CHEMOTHERAPY TREATMENT* (flows f_{ei}, f_{fi} and f_{gi}). The duration of leprosy treatment depends on the type of leprosy at presentation. In SIMLEP, one average treatment duration must be specified per treatment regimen, reflecting the mean treatment duration over the different types of symptomatic leprosy. This duration is converted into a treatment cessation rate; treatment cessation thus does not depend on the bacteriological status of patients. Fixed durations of treatment were not implemented in SIMLEP because of computational complexities. In view of the possibility of endogenous reactivation after cessation of treatment, provision is made for relapses. A new infection can also cause a new episode of symptomatic leprosy after cessation of treatment. In SIMLEP, both options are offered: after cessation of treatment, a fraction can return to the compartment *SUSCEPTIBLE* (flow f_{ib}), and a fraction can move to the compartment *TREATMENT CURED & IMMUNE FOR NEW INFECTIONS* (flow f_{ij}) from which they can experience a relapse to the compartments for symptomatic leprosy (flows f_{je}, f_{jf}, f_{jg}).

A chemotherapy-based control strategy in SIMLEP is characterized by the awareness delay, the reporting delay, the duration of treatment, and relapse rates (if relapses are specified to occur) which are specific for the type of treatment used (dapsone monotherapy or multidrug therapy). Note that since both dapsone and multidrug therapy are assumed to immediately stop the contagiousness of patients, only shorter associated delays in diagnosis and lower relapse rates can render multidrug therapy-based control to be more powerful in reducing transmission than dapsone-based control. Upon cure, individuals either become immune or susceptible for new infections. The corresponding fractions are in SIMLEP independent of the type of treatment. Thus, they are identical for dapsone monotherapy and multidrug therapy. Up to six chemotherapy control strategies can be applied consecutively in one simulation run.

4.4 Example

An example of a simulation run is discussed below in order to show how SIMLEP can be used. As an illustration, a model structure and a set of parameter quantifications have been chosen that in our judgment are not implausible. A simplified model with no *NATURAL IMMUNITY* (no f_{0a}) and with self-healing and treatment cure always being followed by immunity (no f_{db}, f_{eb}, and f_{ib}) is used (Figure 4.2). The parameter quantifications for demography, transmission, course of infection and disease and control strategies are listed in Tables 4.1 and 4.2. In the text below, figures in parentheses denote choices for parameter quantifications.

Input specifications

The stable epidemiological situation at the start of the simulation (1950) has an incidence rate of 2 per 1000 population per year. Demographic data for India for 1976 were used for the birth rate (34.4 per 1000 population) and the life table (Health Monitor, Pune, India: The Foundation for Research in Health Systems, 1993, pages 10, 21). In SIMLEP, the birth rate and life table simulate populations with a constant growth rate and age structure.

By excluding natural immunity, it is assumed that everyone can develop leprosy. The duration of asymptomatic infection is, on average, shorter for those who will not directly develop *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY* than for those who will (Figure 4.3). The average durations are 6.8 and 13.4 years, and the probabilities for this episode to be shorter than 5 years are 73% and 37%, respectively.

Of newly infected individuals, a fraction will self-heal without developing symptomatic leprosy (30%), while the others (70%) will develop symptomatic leprosy. Recovery from an asymptomatic infection, self-healing from symptomatic leprosy, and cure by treatment are assumed to lead to immunity for new leprosy infections (exclusion of flows f_{db}, f_{eb}, and f_{ib}). The proportion among new symptomatic cases developing strong contagiousness *de novo* is relatively small (10%), and cases downgrading at a later stage (30%) will make an important contribution to the pool of strongly contagious individuals. The average duration until self-healing from symptomatic leprosy of 3 years implies that 33% per year will self-heal. Similarly, the annual downgrading rate is 20% per year (or 5 years on average).

All individuals in the compartment *ASYMPTOMATIC INFECTION* are building up contagiousness, and all untreated symptomatic leprosy cases who are not of the *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY* type are weakly contagious. Their relative degree of contagiousness (9%) was calculated in such a way that *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY* cases in total infect four times as many individuals as self-healing cases. In SIMLEP, the strongly contagious cases become gradually less effective in transmitting *M. leprae* (the effectiveness reduces by 50% every 9 months). A "natural" decline in the trend of leprosy incidence is not assumed in the simulation.
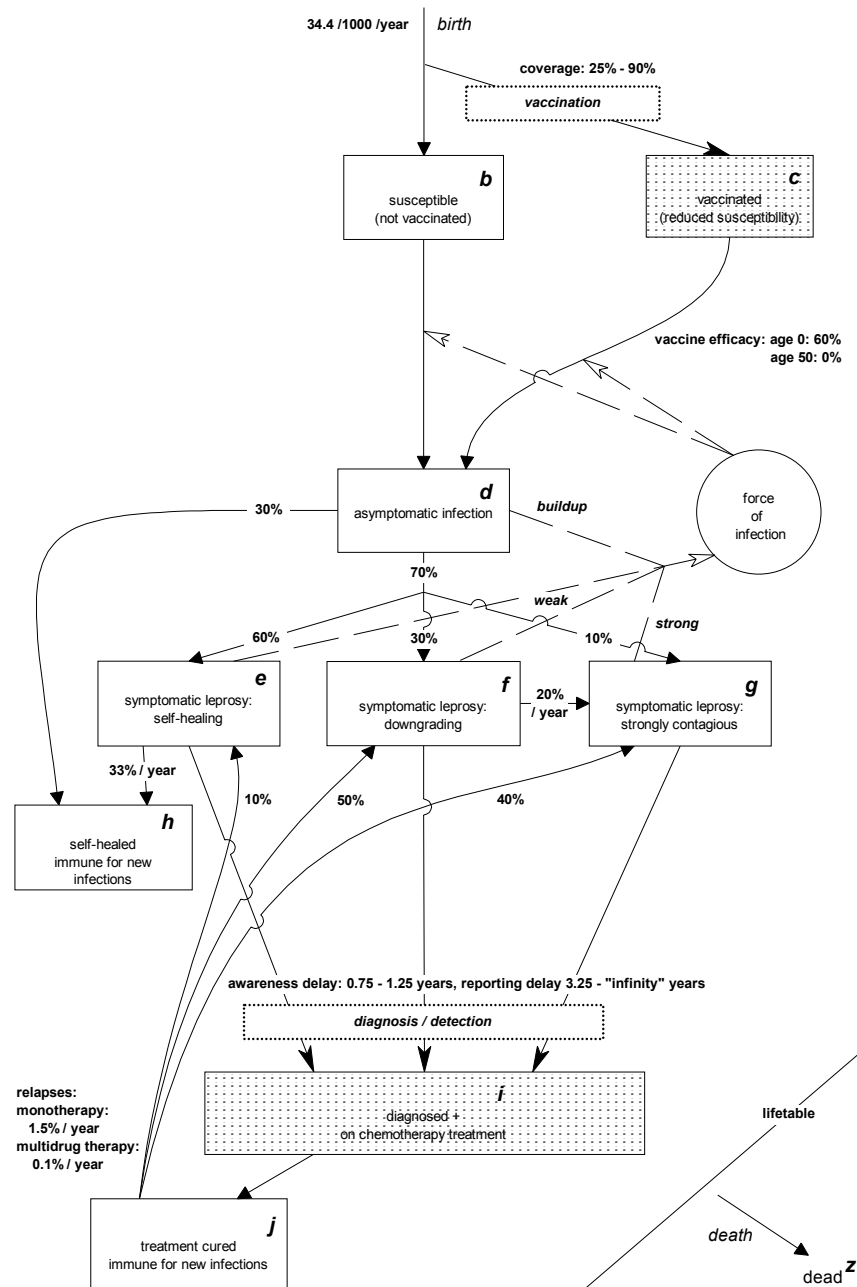
Figure 4.2 Example: Model structure (all ages combined) and parameter specifications.

Table 4.1 Input specifications for the SIMLEP simulation example (see Table 4.2 for control related input).

Input parameter	Flows	Value
Background incidence rate		
Pre-control incidence rate per 1000 total population per year	f_{de}, f_{df}, f_{dg}	2.0
Demographic data		
Birth rate per 1000 total population per year	f_{0a}, f_{0b}, f_{oc}	34.4
Life table	f_{-z}	see text
Natural immunity		
Proportion of newborns who enter NATURAL IMMUNITY	f_{0a}	0%
Asymptomatic infection		
Proportion among newly infected individuals not developing symptomatic leprosy	f_{db}, f_{dh}	30%
Duration of asymptomatic infection	f_{db}, f_{de}, f_{df}, f_{dg}, f_{dh}	see text and Figure 3
Untreated symptomatic leprosy		
Proportion of new cases who (first) to go to		
– SELF-HEALING SYMPTOMATIC LEPROSY	f_{de}	60%
– DOWNGRADING SYMPTOMATIC LEPROSY	f_{df}	30%
– STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY	f_{dg}	10%
Self-healing rate from SELF-HEALING SYMPTOMATIC LEPROSY per year	f_{eb}, f_{eh}	33%
Downgrading rate from DOWNGRADING SYMPTOMATIC LEPROSY per year	f_{fg}	20%
Immunity for new infections upon self-healing	f_{dh}, f_{eh}	100%
Awareness and reporting delays	f_{ei}, f_{fi}, f_{gi}	see Table 2 and Figure 4
Transmission		
Average duration until the transmission of *M. leprae* per unit of time by a strongly contagiousness individual is reduced by 50%	f_{bd}, f_{cd}	0.75 years
Contagiousness for the compartments		
– ASYMPTOMATIC INFECTION		buildup
– SELF-HEALING SYMPTOMATIC LEPROSY	f_{bd}, f_{cd}	weak
– DOWNGRADING SYMPTOMATIC LEPROSY		weak
– STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY		strong
Weighting factor w_{weak}: relative degree of contagiousness (in %) for contagious persons not belonging to STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY	f_{bd}, f_{cd}	9%
Annual secular reduction in the transmission parameter	f_{bd}, f_{cd}	0%

The assumptions on leprosy control are summarized in Table 4.2. BCG, which is administered at birth, has a protective efficacy which by assumption decreases from 60% at age 0 to 0% at age 50 and over. Vaccination starts in 1980, and the coverage increases from 25% in the period 1980-1989 to 75% in 1990 and further to 90% from 1995 onward.

Table 4.2 Input specifications for the SIMLEP simulation example: control related input.

(a) BCG vaccination at birth (flows: f_{ob}, f_{oc}, f_{cd}).

	Period			
	1980-1989	1990	1991-1995	1995-2020
BCG coverage	25%	75%	increases to 90%	90%
Protective efficacy	60% at age 0, decreasing linearly to 50% at age 5, to 25% at age 15, and to 0% for ages 50 and over			

(b) CHEMOTHERAPY: delay until diagnosis (i.e. start of treatment) for SYMPTOMATIC LEPROSY (flows f_{ei}, f_{fi}, f_{gi}).

	Period			
	1955-1960	1960-1990	1990-1993	1993-2020
Average awareness delay (years)	1.25	1.25	decreases to 1	1
Average reporting delay (years)	decreases from "infinity" to 3.25	3.25	decreases to 2	2
Average total delay before starting treatment (years)	decreases from "infinity" to 4.5	4.5	decreases to 3	3

(c) CHEMOTHERAPY: duration of treatment (flows: f_{ib}, f_{ij}).

	Period		
	1955-1990	1990-1998	1998-2020
Average treatment duration (years)	5	0.8	0.2

(d) CHEMOTHERAPY: after cure by treatment.

Input parameter	Flows	Value
Immunity for new infections upon cure by treatment	f_{ij}	100%
Relapse rate after monotherapy cure per year	f_{je}, f_{jf}, f_{jg}	1.5%
Relapse rate after multidrug therapy cure per year	f_{je}, f_{jf}, f_{jg}	0.1%
Proportion of relapsing cases who relapse to (either therapy):		
– SELF-HEALING SYMPTOMATIC LEPROSY	f_{je}	10%
– DOWNGRADING SYMPTOMATIC LEPROSY	f_{jf}	50%
– STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY	f_{jg}	40%

Case detection plus chemotherapy start in 1955. A buildup phase of 5 years is assumed for case detection. The program remains unchanged in the period 1960-1990. The years 1990-1993 reflect a transition phase from dapsone to multidrug therapy during which both the awareness delay and the reporting delay are reduced. The delays again remain unchanged from 1993 onward; see Figure 4.4 for the probability distribution of the total

Probability density
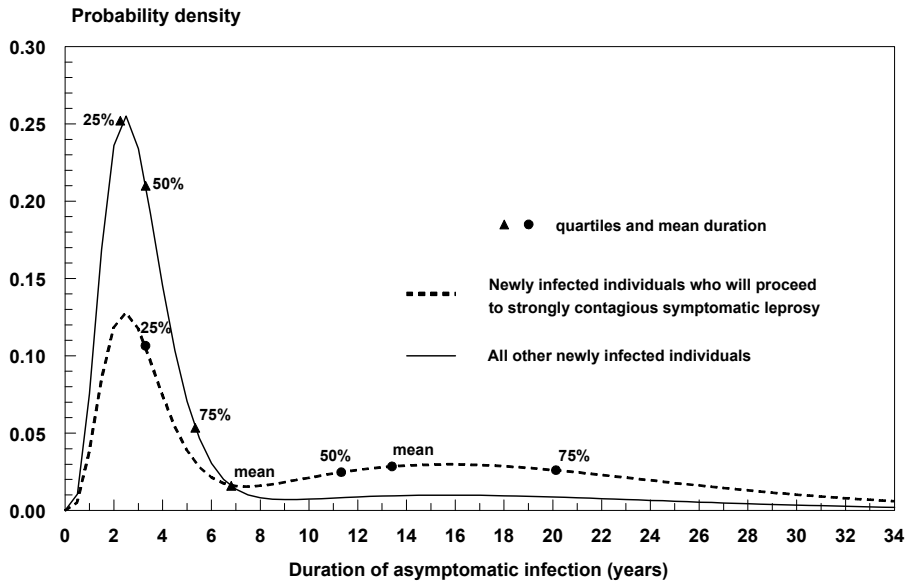
Figure 4.3 Example: Probability density functions for the duration of *ASYMPTOMATIC INFECTION* for those who after this episode directly will proceed to *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY* (the probabilities for this episode to be shorter than 5, 10 and 20 years are, respectively, 37%, 47% and 75%) and those who either will self-heal without showing any sign or symptom of leprosy or will proceed to another expression type of symptomatic leprosy (the corresponding probabilities are 73%, 82% and 92%, respectively).

delay. It has a high variability, with probabilities of 17%, 43%, 86% and 99% that the delay is smaller than 1, 2, 5 and 10 years, respectively. These values apply to all three types of symptomatic leprosy.

The average durations of dapsone treatment, of multidrug therapy, and of the shortened duration of MDT treatment which is postulated from 1998 onward are based on the mix of the different types of symptomatic leprosy considered (the average durations are associated with negative exponential time functions that correspond with treatment completion rates). As mentioned above, cure by treatment in this example implies immunity for new infections (exclusion of flow f_{ib}). Relapse rates after dapsone monotherapy (1.5% per year) are much higher than after multidrug therapy (0.1% per year). The distribution of relapses over the three types of symptomatic leprosy (10%,50%,40%) is in SIMLEP independent of the administered therapy (dapsone monotherapy or multidrug therapy).

Simulation results

The user interface of SIMLEP enables on screen inspection and printing of the output of simulations in both tabular form and through a large number of pre-defined graphs. The

Probability density
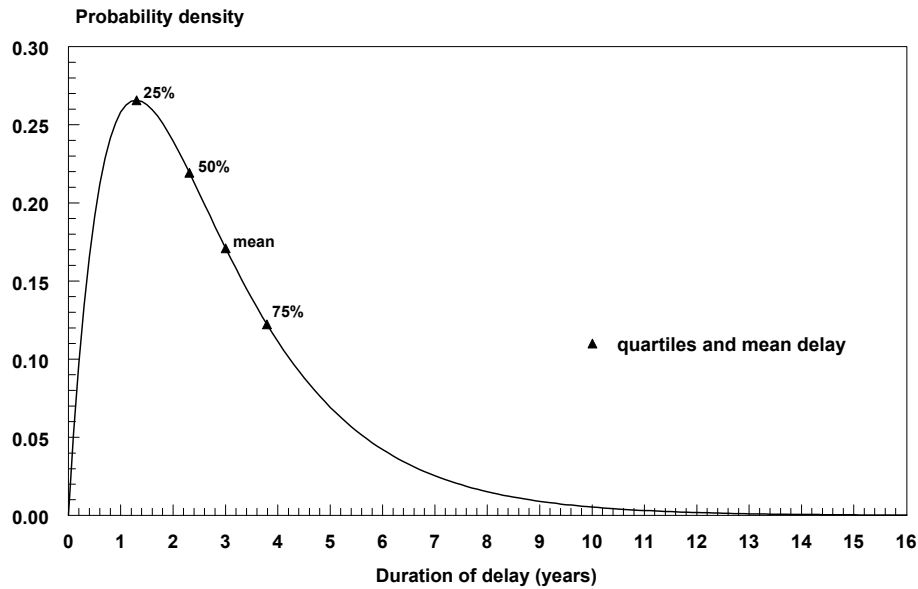
Figure 4.4 Example: Probability density function for the total delay between onset of the first sign or symptom of leprosy and start of chemotherapy during the chemotherapy control strategy over the years 1993-2020 in the example.

pre-defined graphs include both type- and age-specific graphs for the rates of onset of symptomatic leprosy (incidence rate) and of starting chemotherapy treatment of symptomatic leprosy, and for the point prevalences of untreated symptomatic cases and of symptomatic cases on treatment.

Figure 4.5 shows, for the example run, a slow but persistent decrease in the incidence rate from the gradual introduction of dapsone-based control in 1955-1960 onward. The rate of decline increases shortly after 1990 because of the introduction of multidrug therapy and the rise in BCG coverage. The introduction of multidrug therapy is associated with less opportunities for transmission of *M. leprae* due to a (somewhat) earlier detection and its lower relapse rate (relapsed cases contribute to transmission until they again start treatment). The number of cases relapsing after treatment is small as compared to the number of incidence cases. In SIMLEP, case detection only counts when a chemotherapy treatment is started. The early peak in treatment starting rates reflects a clearance of a backlog of untreated cases from the pre-control era. The increase in the treatment starting rate in the transition phase toward multidrug-based control (1990-1993) is explained by earlier detection due to an assumed shortening of the awareness and reporting delays. As a consequence, the gap between the treatment starting rate and the incidence rate becomes smaller (Figure 4.5), and the prevalence of untreated cases declines (Figure 4.6).

Rate per 1000 total population per year
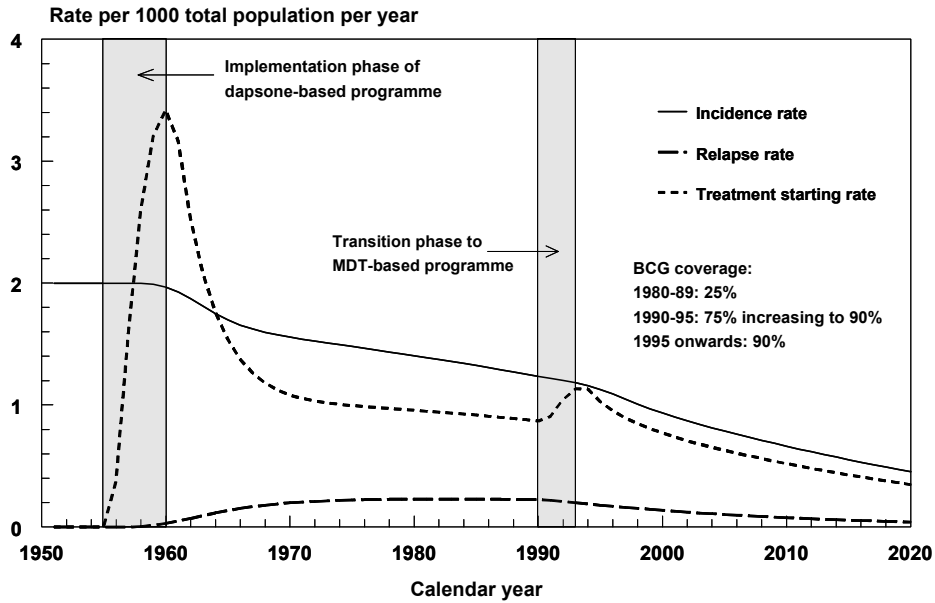
Figure 4.5 Example: Simulated incidence rate of symptomatic leprosy, rate of starting treatment and relapse rate (all expression types of symptomatic leprosy combined).
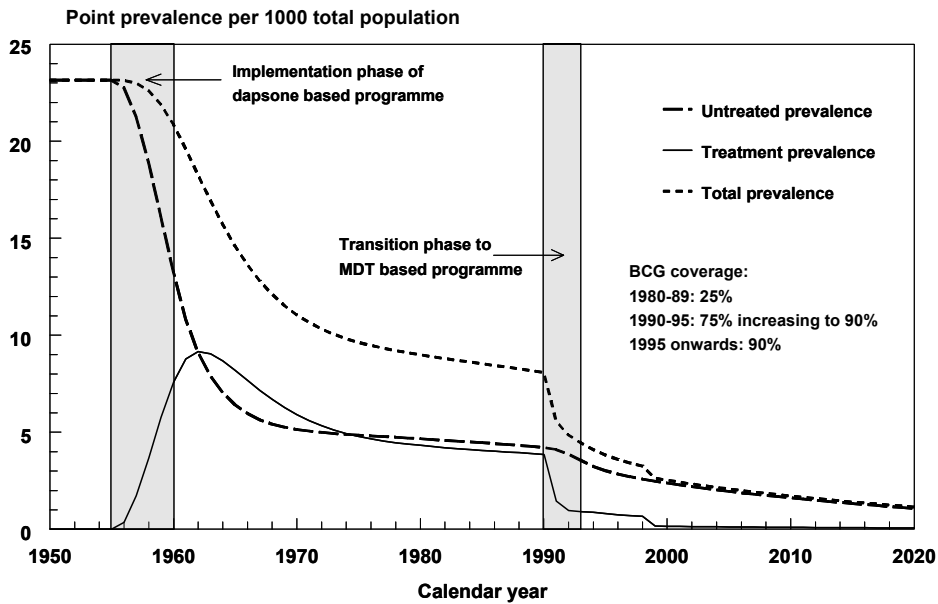
Point prevalence per 1000 total population

Figure 4.6 Example: Simulated point prevalences of untreated symptomatic leprosy, of cases on treatment, and "total" (all types of symptomatic leprosy combined).

In the pre-control period, *STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY* is life-long. Excess mortality due to leprosy is in addition not (yet) included in SIMLEP. The resulting accumulation is the cause of the high prevalence of over 23 per 1000 total population in the pre-dapsone era (Figure 4.6). The clearance of the prevalence pool after the introduction of dapsone gives a rapid fall in the prevalence of untreated cases in the period 1955-1965. Further falls in the total prevalence and in the prevalence of cases on treatment in 1989-1990 and again in 1997-1998 are explained by sudden decreases in the duration of treatment. These reductions lead to less resource requirements and workload in the control program. In the example, the incidence rate (Figure 4.5) and the prevalence of untreated cases (Figure 4.6) are not decreasing very fast, especially because individuals in the compartment *ASYMPTOMATIC INFECTION* build up contagiousness before diagnosis takes place.

4.5 Discussion

In developing the SIMLEP simulation model we made choices regarding aspects to be included and their level of detail, keeping in mind the objectives of SIMLEP: to be a useful tool in analyzing leprosy data and, in particular, to be valuable in predicting the effects of existing and potential control policies.

Both objectives require characterization of processes underlying leprosy transmission. Several aspects relating to susceptibility and transmission are included: natural immunity, asymptomatic infections, differences in contagiousness between asymptomatic and symptomatic stages, and the decline in effective contagiousness over time. This decline reflects that household and other frequent contacts of highly contagious cases are probably already infected during the period shortly after the index case became contagious.

A central issue is the impact of control on transmission. Control options can be described while taking into account limitations in their effectiveness. When specifying a SIMLEP vaccination program, one may account for incomplete coverage, less than 100% protective efficacy, and waning of protection over time. The influence of a control program on case detection can be simulated by its impact on two consecutive delays. The delays can be thought to represent becoming aware of leprosy symptoms and reporting the disease, respectively. The delays may, for example, decrease when short-term chemotherapy is introduced. Provisions for relapse and for susceptibility to new infections following cure limit the effectiveness of chemotherapy control. SIMLEP produces output on trends in age-specific prevalence, incidence and case detection rates in order to study the impact of the interventions vaccination, case detection and chemotherapy treatment.

SIMLEP can assist in clarifying basic mechanisms that govern transmission and the natural history of leprosy as well as the impact of control. One could argue that the present structure of SIMLEP is too complex for this type of application. However, the

user may simplify the model structure within the SIMLEP framework according to his or her requirements. By selectively inactivating flows and compartments from the full SIMLEP structure, much simpler models can be simulated. For example, it is possible to simulate chemotherapy control strategies using a model with only the five compartments *SUSCEPTIBLE, ASYMPTOMATIC INFECTION, SELF-HEALING SYMPTOMATIC LEPROSY, STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY* and *DIAGNOSED + ON CHEMOTHERAPY TREATMENT* of Figure 4.1.

On the other hand, SIMLEP may not be sufficiently comprehensive. Model extensions that are required when specific questions are addressed may often be incorporated in SIMLEP. Examples are excess mortality, separate contagiousness of self-healing infections, drug resistance and prolonged contagiousness after initiation of chemotherapy. The same applies to the distinction between males and females which is not yet included. But increasing the number of aspects covered in a compartment model such as SIMLEP quickly leads to an explosion of the number of states in the computer program, leading to unrealistic requirements regarding computer power. The population-based simulation of compartments also prohibits incorporation of certain aspects. This particularly applies to provisions for explicit and detailed modeling of high transmission risks in small groups such as households, or detailed modeling of individual (genetic / hereditary) differences in susceptibility, which require individual-based simulation. Note that these kinds of heterogeneity can substantially influence the age distribution of prevalence, incidence and case detection rates, and the impact of interventions on transmission.

Quantification and validation

Proper validation of a model is crucial for its usefulness as a tool for prediction, evaluation, and planning. Uncertainty about the validity of SIMLEP refers to both the structure of the model and to the quantification of the individual parameters, and reflects the state of knowledge on leprosy. This uncertainty is shared with any other approach to produce statements on leprosy epidemiology and its control. Levels of uncertainty about model parameters vary with the amount and quality of pertinent data that can be used for testing and quantifying assumptions. The age structure and life table can be obtained from demographic data which are available for most regions. Program registries give information on the type distribution of new symptomatic cases according to type of leprosy at the time of detection. Relapse rates after cure by dapsone monotherapy and multidrug therapy have been documented (*23*). Some data are also available on self-healing and downgrading rates (*21, 24*). Crude estimates on delays between onset of disease and start of chemotherapy have been obtained in several control programs by interviewing patients (e.g. (*25-28*)). Vaccine trials give information on the extent to which vaccines can prevent new cases of leprosy (*3*) .

There are also parameters for which it is much more difficult, if not impossible, to collect data. Due to a lack of diagnostic tools to establish *M. leprae* infection, knowledge is in particular limited on the incubation period, on the occurrence of asymptomatic infections

and natural immunity, and on leprosy transmission. The flexibility in SIMLEP can be used to explore and test a broad range of assumptions about transmission. The example can be used to illustrate that different combinations of assumptions may describe trend data equally well. We assumed that natural immunity does not occur, and that all individuals who have asymptomatic or symptomatic leprosy infections are contagious. However, the incidence rates in the pre-control period and in 1990, as shown in Figure 4.5, can also be obtained when 80% natural immunity is assumed among newborns or when contagiousness is assumed to be restricted to strongly contagious leprosy cases only, with simultaneous adaptation of transmission parameters, such as the level of weak contagiousness, the half-life time of the effectiveness in transmitting *M. Leprae* for strongly contagious individuals, and the contagiousness of a strongly contagious individual as expressed by SIMLEP's internal transmission parameter β.

Further confidence in the model is to be gained from extensive validation studies in which detailed data sets are being used. At present, SIMLEP is being validated on the long-term data describing the decline of leprosy in Norway between 1850 and 1920 (*29*). Model assumptions will be checked against age-specific information on trends in prevalence, incidence and case detection of leprosy by calendar year and birth cohort, using available information on the reporting delay and on changes in proportions of patients being isolated. Trends will be analyzed for areas with different initial endemicity levels in 1850.

The mid-term and long-term impact of intensified case finding plus MDT treatment on leprosy transmission is still unclear. The transition phase from dapsone-based to MDT-based programs often goes hand in hand with intensification of case detection efforts, which may lead to increasing new case detection rates, even if incidence rates are declining. Benefits of this change in policy in terms of reductions in leprosy transmission may also not directly be visible due to the long incubation period of leprosy. Further validation studies will be targeted at describing the impact of leprosy control (including BCG vaccination). The uncertainty about model assumptions, especially relating to leprosy transmission, can potentially be narrowed down by comparing SIMLEP results with data from recent intervention studies (e.g. (*3, 30, 31*)). These further validation studies are essential in making SIMLEP a useful tool for prospectively evaluating alternative intervention policies.

Contribution to policy discussion

Policy makers and epidemiologists face large gaps in knowledge about leprosy. Still, policy makers have to make decisions about leprosy control, and epidemiologists and leprosy experts are sometimes tempted to make quite forthright forecasts on future incidence and prevalence of leprosy (*4*). The SIMLEP example tried by us suggests that it may not be easy to achieve rapid declines in leprosy transmission through intensified case finding plus MDT. In situations like this that are fraught with uncertainties, a simulation model like the present SIMLEP can be a useful, independent input in rational reasoning about

leprosy. When experts and decision makers specify their knowledge and uncertainties about aspects of leprosy, the model can be used to predict the range of possible effects of these options. In future, we will analyze how sensitive predictions of trends and effects of control policies are for variations in the input parameters, and will identify those uncertain parameters that affect the predictions most.

4.6 Acknowledgments

4.7 References

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4A Mathematical appendix

This appendix gives a complete description of the SIMLEP model. Compartment names in this appendix refer to the flowchart (Figure 4.1) and are given in capital. Some compartments have been split up in sub-compartments in order to allow sojourn time distributions other than negative exponential and in order to allow the effectiveness of contagiousness to reduce over time. A complete set of equations describing the model is given at the end of this appendix.

The sub-compartments $D^{i,j}$ (i=1,2,j=1,..5), E^1, E^2, F^1, F^2, G^1, G^2, G^3, G^4, J^1 and J^2

Upon infection, individuals enter the compartment D which represents the asymptomatic period. This compartment is divided into two parallel chains of five successive stages (sub-compartments) with equal transition rates within each chain. This results in ten sub-compartments $D^{i,j}$ (i = 1,2,j = 1,..5) with two transition rates λ_i (i = 1,2).

The compartments SELF-HEALING SYMPTOMATIC LEPROSY (E) and DOWNGRADING SYMPTOMATIC LEPROSY (F) have been split up in E^1 and F^1 for individuals who are not (yet) aware of their disease, and E^2 and F^2 for individuals who have become aware of their disease. The compartment STRONGLY CONTAGIOUS SYMPTOMATIC LEPROSY (G) is also subdivided to allow for individuals who are and who are not aware of their disease. In addition, G is further subdivided into a category in which contagiousness is still fully effective, and a category for individuals with zero effectivity in transmitting $M.$ $leprae$. Thus, G consists in fact of the following four sub-compartments:

- G^1 not aware of disease, full effectivity of contagiousness
- G^2 not aware of disease, zero effectivity of contagiousness
- G^3 aware of disease, full effectivity of contagiousness
- G^4 aware of disease, zero effectivity of contagiousness.

Individuals shift from full to zero effectivity of contagiousness with a transition rate $\lambda_{foi\ loss}$. The average contagiousness c_{loss} of all people in G (see main text) is the weighted average of the effectivity of contagiousness of individuals in the compartments G^1 and G^3 (full effectivity), and G^2 and G^4 (zero effectivity). Formulae for the force of infection are given elsewhere in this appendix.

SIMLEP distinguishes two relapse rates, one for monotherapy, and one for multidrug therapy. The compartment J for individuals who are cured by treatment, and who are immune for new infections, but who can relapse, is split up accordingly: J^1 comprises individuals who have been cured by monotherapy (corresponding relapse rate $\lambda_{relapse,1}$), and J^2 reflects cure by multidrug therapy (corresponding relapse rate $\lambda_{relapse,2}$).

Transition rates and probabilities for transitions from compartments

Transitions from most compartments are governed by transitions rates. SIMLEP applies the following transition rates:

λ_i = rate of leaving the present sub-compartment of asymptomatic infection ($i = 1,2$)

λ_{heal} = rate of self-healing from E^1 and E^2

λ_{downgr} = rate of downgrading from F^1 and F^2 to G^3

$\lambda_{foi\ loss}$ = rate of losing capability to transmit *M. leprae* for individuals in G^1 and G^3

$\lambda_{aware,X,t}$ = rate of becoming aware of disease under the control strategy at time t

$\quad\quad\quad (X = E^1,F^1,G^1,G^2)$

$\lambda_{chemo,X,t}$ = rate of reporting for treatment when being aware of disease under the control

$\quad\quad\quad$ strategy at time t $\quad (X = E^2,F^2,G^3,G^4)$

$\lambda_{cure,t}$ = cure rate for drug regimen used under control strategy at time t

$\lambda_{relapse,J^1}$ = relapse rate after dapsone monotherapy cure (relapse occurs from J^1)

$\lambda_{relapse,J^2}$ = relapse rate after multidrug therapy cure (relapse occurs from J^2)

SIMLEP is a discrete time simulation model in which people can only make one transition per time step, and in fact calculates transitions according to transition probabilities. For some compartments people can only move to one subsequent compartment. The probability p for occurrence of such a transition during a time step Δt and the corresponding transition rate λ are interrelated through the negative exponential distribution via $p = 1 - e^{-\lambda \cdot \Delta t}$. The corresponding average sojourn time d (in years) in such a compartment is given by $d = \Delta t / p$.

For a number of compartments, transitions to different destinations are possible because several events can occur. For these compartments, transition probabilities are derived by combining the negative exponential distribution functions that correspond with the transition rates. The exact formulae for each compartment are given at the end of this appendix. Three combination rules are possible:

- the event that takes place first may determine the destination, e.g. self-healing or starting chemotherapy: see the equations for $p_{heal,E^2,t}$ and $p_{chemo,E^2,t}$

- some events rule out others, e.g. becoming aware of disease is irrelevant if self-healing occurs in the same time step: see the equations for $p_{heal,E^1,t}$ and $p_{chemo,E^1,t}$

- events can occur independently of each other in the same time step without excluding each other, e.g. becoming aware of disease and losing effectiveness of contagiousness: see the equations for $p_{foiloss,G^1,t}$, $p_{aware,G^1,t}$ and $p_{both,G^1,t}$.

The average sojourn time in compartments from which multiple transitions are possible follows from the sums of the probabilities for these transitions to take place.

Probabilities for determining the destination of transitions which do not depend on transition rates

At birth, people can move to one of several compartments. Similarly, relapses can take place to each of the three types of symptomatic leprosy. The user can specify probabilities that determine the destination of such transitions.

The two chains of subcompartments $D^{1,j}$ and $D^{2,j}$ represent the slow and fast asymptomatic stages, respectively. The user specified probabilities $q_{\neq G}$ and q_G denote the probability of having a "short" asymptomatic period, i.e. of entering $D^{1,1}$ upon infection. Probability $q_{\neq G}$ applies to individuals who would eventually move to the compartment G^1 and probability q_G applies to individuals who would move to one of the other compartments (B,E^1,F^1 or H). The user also specifies the transition probabilities q_{DX} which denote the probability that newly infected individuals who enter compartment D would eventually transfer to compartment X ($X=B,E^1,F^1,G^1,H$). These individuals may however die during their stay in compartment D. SIMLEP therefore derives probabilities $q_{DX}^{1,5}$ and $q_{DX}^{2,5}$ for transfering to compartment X ($X=B,E^1,F^1,G^1,H$) upon having passed through (and having survived) the five stages of either chain. SIMLEP calculates these probabilities $q_{DX}^{1,5}$ and $q_{DX}^{2,5}$ from the probabilities q_{DX}, $q_{\neq G}$ and q_G ($X=B,E^1,F^1,G^1,H$).

Summarizing, the probabilities which directly determine transition destinations and which do not depend on the transition rates are:

q_{0A} = fraction of newborns having (life-long) natural immunity

$q_{cov,t}$ = vaccination coverage among newborns at time t

$q_{prot,a}$ = protective vaccine efficacy against leprosy infection at age a

　　　　　($q_{prot,a}$ is a piece-wise linear function of age)

$q_{\neq G}$ = probability to transfer to $D^{1,1}$, and hence not to $D^{2,1}$, upon infection

　　　　　(for a priori destination : B, E^1, F^1 or H)

q_G = probability to transfer to $D^{1,1}$, and hence not to $D^{2,1}$, upon infection

　　　　　(for a priori destination : G^1)

q_{DX} = user-defined probability of eventually transfering to X after asymptomatic period

　　　　　($X = B, E^1, F^1, G^1, H$; $q_{DB} + q_{DE^1} + q_{DF^1} + q_{DG^1} + q_{DH} = 1$)

q_{all} = $(q_{DB} + q_{DE^1} + q_{DF^1} + q_{DH}) \cdot q_{\neq G} + q_{DG^1} \cdot q_G$

　　　　　= probability to transfer to $D^{1,1}$ for an arbitrary newly infected individual

$q_{DX}^{1,5}$ = $\begin{cases} q_{DX} \cdot q_{\neq G} / q_{all} = \text{probability to transfer from } D^{1,5} \text{ to } X \ (X = B, E^1, F^1, H) \\ q_{DG} \cdot q_G / q_{all} = \text{probability to transfer from } D^{1,5} \text{ to } G \end{cases}$

$q_{DX}^{2,5}$ = $\begin{cases} q_{DX} \cdot (1 - q_{\neq G}) / (1 - q_{all}) = \text{probability to transfer from } D^{2,5} \text{ to } X \ (X = B, E^1, F^1, H) \\ q_{DG} \cdot (1 - q_G) / (1 - q_{all}) = \text{probability to transfer from } D^{2,5} \text{ to } G \end{cases}$

q_{EX} = probability to transfer to X upon self-healing from E^1 and E^2

　　　　　($X = B, H$; $q_{EB} + q_{EH} = 1$)

q_{IX} = probability to transfer to X upon treatment cure ($X = B, J$; $q_{IB} + q_{IJ} = 1$)

q_{JX} = probability to transfer to X upon relapsing ($X = E^1, F^1, G^1$; $q_{JE^1} + q_{JF^1} + q_{JG^1} = 1$)

The force of infection

G^1 and G^3 are by definition contagious, and G^2 and G^4 are not. Indicator functions indicate which of the compartments E^1, E^2, F^1 and F^2 have been specified to be (weakly) contagious, and for which destinations (E^1, F^1, G^1, and B or H) buildup of contagiousness during the asymptomatic period D has been specified. An initial number of the sub-compartments $D^{1,j}$ and $D^{2,j}$ can still be specified to be non-contagious when buildup of contagiousness is assumed. The contagiousness is assumed to increase step-wise over the remainder of the five sub-compartments. This is taken care of through the function $w_{buildup}$. The force of infection FOI_t at time t involves the transmission parameter β, weights for the relative contagiousness of individuals, numbers of individuals in the compartments that are contagious, and the total population size N_t at time t. In formula:

$$FOI_t \quad = \quad \beta \cdot (1-\mu)^{t-t_0} \cdot \frac{\sum_a Y_{a,t}}{N_t}$$

with

a = age

β = transmission parameter

μ = annual reduction factor for transmission parameter β

t_0 = the annual reduction factor μ applies from time t_0 onwards

w_{weak} = level of contagiousness relative to initial level of contagiousness in G

n_b = number of stages out of 5 during which contagiosness builds up in D ($0 \le n_b \le 5$)

$\quad$ ($n_b = 0$ is equivalent to complete absence of contagiousness in D)

$w_{buildup}^{j,n_b}$ = contagiousness build-up factor for $D^{1,j}$ and $D^{2,j}$:

$$w_{buildup}^{j,n_b} = \begin{cases} = 0 \;\; \text{if} \;\; j \le 5 - n_b \quad (j=1,2,..,5) \\ = (j - 5 + n_b)\,/\,(n_b + 1) \;\; \text{otherwise} \quad (j=1,2,..,5) \end{cases}$$

i_{DBH} = 0 if those developing asymptomatic infection only are not contagious, 1 otherwise

i_{DX} = 0 if those proceeding to X do not build up contagiousness, 1 otherwise

$\quad$ ($X = E^1, F^1, G^1$)

i_X = 0 if those in X are (weakly) contagious, 1 otherwise

$\quad$ ($X = E, F$) with $E = E^1 \cup E^2$, $F = F^1 \cup F^2$

$Y_{a,t}$ = $G_{a,t}^1 + G_{a,t}^3 + w_{weak} \cdot \left[i_E \cdot (E_{a,t}^1 + E_{a,t}^2) + i_F \cdot (F_{a,t}^1 + F_{a,t}^2) \right] + \sum_{j=1}^5 w_{weak} \cdot w_{buildup}^{j,n_b} \cdot$

$\quad \left[i_{DBH} \cdot (q_{DB} + q_{DH}) + i_{DE} \cdot q_{DE} + i_{DF} \cdot q_{DF} \right] \cdot \left[q_{\ne G} \cdot D_{a,t}^{1,j} \,/\, q_{all} + (1 - q_{\ne G}) \cdot D_{a,t}^{2,j} \,/\, (1 - q_{all}) \right]$

$\quad + \sum_{j=1}^5 w_{buildup}^{j,n_b} \cdot i_{DG^1} \cdot q_{DG^1} \cdot \left[q_G \cdot D_{a,t}^{1,j} \,/\, q_{all} + (1 - q_G) \cdot D_{a,t}^{2,j} \,/\, (1 - q_{all}) \right]$

N_t = $\sum_a \left[A_{a,t} + B_{a,t} + C_{a,t} + \sum_{i=1}^2 \left(\sum_{j=1}^5 D_{a,t}^{i,j} + E_{a,t}^i + F_{a,t}^i \right) + \sum_{i=1}^4 G_{a,t}^i + H_{a,t} + I_{a,t} + J_{a,t}^1 + J_{a,t}^2 \right]$

The order of calculations for birth, death, ageing and transitions between compartments

At each time step, the compartments are first updated for the transitions that take place between them. Next, the updated compartments are corrected for deaths that occur during the time step.

Then, the age of the remaining (surviving) individuals is increased by one time step, and the newborns enter into the system with initial age 0. The number of newborns is calculated by multiplying the model parameter b (number of births per head of population per year) with the average of the population sizes before and after death, and with the length of the simulation time step Δt. In the set of difference equations given below a simplified notation is used which does neither express this order of calculations nor the averaging of the population size before and after death for calculating the number of births in the time step.

The set of difference equations for SIMLEP

The following notations are used in the set of difference equations:

t	$=$	time
Δt	$=$	length of a time step
b	$=$	number of births per head of population per year
d_a	$=$	probability of dying at age a given survival up to age a
a	$=$	age
$i_{chemo,t}$	$=$	0 if the drug regimen at time t is dapsone, 1 otherwise

Transition probabilities and transition rates are inter-related as follows:

$$p_1 = 1 - e^{-\lambda_1 \cdot \Delta t}$$

$$p_2 = 1 - e^{-\lambda_2 \cdot \Delta t}$$

$$p_{heal,E^1,t} = 1 - e^{-\lambda_{heal} \cdot \Delta t}$$

$$p_{aware,E^1,t} = e^{-\lambda_{heal} \cdot \Delta t} \cdot \left[1 - e^{-\lambda_{aware,E,t} \cdot \Delta t} \right]$$

$$p_{heal,E^2,t} = \frac{\lambda_{heal}}{\lambda_{heal} + \lambda_{chemo,E,t}} \cdot \left[1 - e^{-(\lambda_{heal} + \lambda_{chemo,E,t}) \cdot \Delta t} \right]$$

$$p_{chemo,E^2,t} = \frac{\lambda_{chemo,E,t}}{\lambda_{heal} + \lambda_{chemo,E,t}} \cdot \left[1 - e^{-(\lambda_{heal} + \lambda_{chemo,E,t}) \cdot \Delta t} \right]$$

$$p_{downgr,F^1,t} = 1 - e^{-\lambda_{downgr} \cdot \Delta t}$$

$$p_{aware,F^1,t} = e^{-\lambda_{downgr} \cdot \Delta t} \cdot \left[1 - e^{-\lambda_{aware,F,t} \cdot \Delta t} \right]$$

$$p_{downgr,F^2,t} = e^{-\lambda_{chemo,F,t} \cdot \Delta t} \cdot \left[1 - e^{-\lambda_{downgr} \cdot \Delta t} \right]$$

$$p_{chemo,F^2,t} = 1 - e^{-\lambda_{chemo,F,t} \cdot \Delta t}$$

$$p_{foi\,loss,G^1,t} = e^{-\lambda_{aware,G,t} \cdot \Delta t} \cdot \left[1 - e^{-\lambda_{foi\,loss} \cdot \Delta t} \right]$$

$$p_{aware,G^1,t} = e^{-\lambda_{foi\,loss} \cdot \Delta t} \cdot \left[1 - e^{-\lambda_{aware,G,t} \cdot \Delta t} \right]$$

$$p_{both,G^1,t} = \left[1 - e^{-\lambda_{foi\,loss} \cdot \Delta t} \right] \cdot \left[1 - e^{-\lambda_{aware,G,t} \cdot \Delta t} \right]$$

$$p_{aware,G^2,t} = 1 - e^{-\lambda_{aware,G,t} \cdot \Delta t}$$

$$p_{foi\,loss,G^3,t} = e^{-\lambda_{chemo,G,t} \cdot \Delta t} \cdot \left[1 - e^{-\lambda_{foi\,loss} \cdot \Delta t} \right]$$

$$p_{chemo,G^3,t} = p_{chemo,G^4,t} = 1-e^{-\lambda_{chemo,G,t}\cdot\Delta t}$$

$$p_{cure,I,t} = 1-e^{-\lambda_{cure,t}\cdot\Delta t}$$

$$p_{relapse,J^1} = 1-e^{-\lambda_{relapse,1}\cdot\Delta t}$$

$$p_{relapse,J^2} = 1-e^{-\lambda_{relapse,2}\cdot\Delta t}$$

The resulting set of difference equations for SIMLEP is as follows (the superscript [1] of the compartments E^1, F^1 and G^1 is omitted in destination probabilities q of transitions to these compartments):

$$\Delta A_{a,t} = q_{0A}\cdot b\cdot N_t\cdot\Delta t - d_a\cdot A_{a,t}\cdot\Delta t$$

$$\Delta B_{a,t} = (1-q_{0A})\cdot(1-q_{cov,t})\cdot b\cdot N_t\cdot\Delta t + \sum_{i=1}^{2}q_{DB}^{i,5}\cdot p_i\cdot D_{a,t}^{i,5}$$
$$+ q_{EB}\cdot(p_{heal,E^1,t}\cdot E_{a,t}^1 + p_{heal,E^2,t}\cdot E_{a,t}^2) + q_{IB}\cdot p_{cure,I,t}\cdot I_{a,t} - FOI_t\cdot B_{a,t}\cdot\Delta t - d_a\cdot B_{a,t}\cdot\Delta t$$

$$\Delta C_{a,t} = (1-q_{0A})\cdot q_{cov,t}\cdot b\cdot N_t\cdot\Delta t - (1-q_{prot,a})\cdot FOI_t\cdot C_{a,t}\cdot\Delta t - d_a\cdot C_{a,t}\cdot\Delta t$$

$$\Delta D_{a,t}^{1,1} = FOI_t\cdot q_{all}\cdot(B_{a,t}+(1-q_{prot,a})\cdot C_{a,t})\cdot\Delta t - p_1\cdot D_{a,t}^{1,1} - d_a\cdot D_{a,t}^{1,1}\cdot\Delta t$$

$$\Delta D_{a,t}^{2,1} = FOI_t\cdot(1-q_{all})\cdot(B_{a,t}+(1-q_{prot,a})\cdot C_{a,t})\cdot\Delta t - p_2\cdot D_{a,t}^{2,1} - d_a\cdot D_{a,t}^{2,1}\cdot\Delta t$$

$$\Delta D_{a,t}^{i,j} = p_i\cdot D_{a,t}^{i,j-1} - p_i\cdot D_{a,t}^{i,j} - d_a\cdot D_{a,t}^{i,j}\cdot\Delta t \quad (i=1,2,\ j=2,...,5)$$

$$\Delta E_{a,t}^1 = \sum_{i=1}^{2}q_{DE}^{i,5}\cdot p_i\cdot D_{a,t}^{i,5} + q_{JE}\cdot(p_{relapse,J^1}\cdot J_{a,t}^1 + p_{relapse,J^2}\cdot J_{a,t}^2) - p_{heal,E^1,t}\cdot E_{a,t}^1$$
$$- p_{aware,E^1,t}\cdot E_{a,t}^1 - d_a\cdot E_{a,t}^1\cdot\Delta t$$

$$\Delta E_{a,t}^2 = p_{aware,E^1,t}\cdot E_{a,t}^1 - p_{heal,E^2,t}\cdot E_{a,t}^2 - p_{chemo,E^2,t}\cdot E_{a,t}^2 - d_a\cdot E_{a,t}^2\cdot\Delta t$$

$$\Delta F_{a,t}^1 = \sum_{i=1}^{2}p_i\cdot q_{DF}^{i,5}\cdot D_{a,t}^{i,5} + q_{JF}\cdot(p_{relapse,J^1}\cdot J_{a,t}^1 + p_{relapse,J^2}\cdot J_{a,t}^2) - p_{downgr,F^1,t}\cdot F_{a,t}^1$$
$$- p_{aware,F^1,t}\cdot F_{a,t}^1 - d_a\cdot F_{a,t}^1\cdot\Delta t$$

$$\Delta F_{a,t}^2 = p_{aware,F^1,t}\cdot F_{a,t}^1 - p_{downgr,F^2,t}\cdot F_{a,t}^2 - p_{chemo,F^2,t}\cdot F_{a,t}^2 - d_a\cdot F_{a,t}^2\cdot\Delta t$$

$$\Delta G_{a,t}^1 = \sum_{i=1}^{2}q_{DG}^{i,5}\cdot p_i\cdot D_{a,t}^{i,5} + q_{JG}\cdot(p_{relapse,J^1}\cdot J_{a,t}^1 + p_{relapse,J^2}\cdot J_{a,t}^2) - p_{aware,G^1,t}\cdot G_{a,t}^1$$
$$- p_{foi\,loss,G^1,t}\cdot G_{a,t}^1 - p_{both,G^1,t}\cdot G_{a,t}^1 - d_a\cdot G_{a,t}^1\cdot\Delta t$$

$$\Delta G_{a,t}^2 = p_{foi\,loss,G^1,t}\cdot G_{a,t}^1 - p_{aware,G^2,t}\cdot G_{a,t}^2 - d_a\cdot G_{a,t}^2\cdot\Delta t$$

$$\Delta G_{a,t}^3 = p_{downgr,F^1,t}\cdot F_{a,t}^1 + p_{downgr,F^2,t}\cdot F_{a,t}^2 + p_{aware,G^1,t}\cdot G_{a,t}^1 - p_{foi\,loss,G^3,t}\cdot G_{a,t}^3$$
$$- p_{chemo,G^3,t}\cdot G_{a,t}^3 - d_a\cdot G_{a,t}^3\cdot\Delta t$$

$$\Delta G_{a,t}^4 = p_{both,G^1,t}\cdot G_{a,t}^1 + p_{aware,G^2,t}\cdot G_{a,t}^2 + p_{foi\,loss,G^3,t}\cdot G_{a,t}^3 - p_{chemo,G^4,t}\cdot G_{a,t}^4 - d_a\cdot G_{a,t}^4\cdot\Delta t$$

$$\Delta H_{a,t} = \sum_{i=1}^{2}(1-q_{DB}^{i,5}-q_{DE}^{i,5}-q_{DF}^{i,5}-q_{DG}^{i,5})\cdot p_i\cdot D_{a,t}^{i,5} + q_{EH}\cdot(p_{heal,E^1,t}\cdot E_{a,t}^1 + p_{heal,E^2,t}\cdot E_{a,t}^2)$$
$$- d_a\cdot H_{a,t}\cdot\Delta t$$

$$\Delta I_{a,t} = p_{chemo,E^2,t}\cdot E_{a,t}^2 + p_{chemo,F^2,t}\cdot F_{a,t}^2 + p_{chemo,G^3,t}\cdot G_{a,t}^3 + p_{chemo,G^4,t}\cdot G_{a,t}^4 - p_{cure,I,t}\cdot I_{a,t}$$
$$- d_a\cdot I_{a,t}\cdot\Delta t$$

$$\Delta J_{a,t}^1 = (1-i_{chemo,t})\cdot q_{IJ}\cdot p_{cure,I,t}\cdot I_{a,t} - p_{relapse,J^1}\cdot J_{a,t}^1 - d_a\cdot J_{a,t}^1\cdot\Delta t$$

$$\Delta J_{a,t}^2 = i_{chemo,t}\cdot q_{IJ}\cdot p_{cure,I,t}\cdot I_{a,t} - p_{relapse,J^2}\cdot J_{a,t}^2 - d_a\cdot J_{a,t}^2\cdot\Delta t$$

5

Disappearance of leprosy from Norway: an exploration of critical factors using an epidemiological modelling approach

5.1 Summary

Background By the middle of the 19th century, leprosy was a serious public health problem in Norway. By 1920, new cases only rarely occurred. This study aims to explain the disappearance of leprosy from Norway.

Methods Data from the National Leprosy Registry of Norway and population censuses were used. The patient data include year of birth, onset of disease, registration, hospital admission, death, and emigration. The Norwegian data were analysed using epidemiological models of disease transmission and control.

Results The time trend in leprosy new case detection in Norway can be reproduced adequately. The shift in new case detection towards older ages which occurred over time is accounted for by assuming that infected individuals may have a very long incubation period. The decline cannot be explained fully by the Norwegian policy of isolation of patients: an autonomous decrease in transmission, reflecting improvements in for instance living conditions, must also be assumed. The estimated contribution of the isolation policy to the decline in new case detection very much depends on assumptions made on build-up of contagiousness during the incubation period and waning of transmission opportunities due to rapid transmission to close contacts.

Conclusion The impact of isolation on interruption of transmission remains uncertain. This uncertainty also applies to contemporary leprosy control that mainly relies on chemotherapy treatment. Further research is needed to establish the impact of leprosy interventions on transmission.

5.2 Keywords

computer simulation, epidemiology, history, leprosy, Norway, patient isolation

5.3 Introduction

Founded in 1856, the National Leprosy Registry of Norway documents the fall of leprosy in Norway. By 1920, new cases were only rarely detected. On the basis of the registry, Irgens analysed the disappearance of leprosy from Norway (*1*). Between 1856 and 1920, the new case detection rate steadily declined, whereas the ages of newly detected cases gradually but distinctly increased. The decline of leprosy coincided with changes in a number of factors which may influence the occurrence of leprosy and it has been shown to be associated with the policy of isolation of patients in hospitals which was implemented in Norway (*1*). The decline took place long before effective anti-leprosy treatment became available.

Leprosy epidemiology is fraught with many uncertainties. In particular, knowledge on the relative contagiousness of different stages of leprosy is lacking. The uncertainties make it difficult to assess the impact of interventions on time trends in leprosy, especially when other factors influencing leprosy change simultaneously. Simulation models can help to organize knowledge and assumptions on diseases, and enable exploration of the occurrence of diseases in populations over time. This study uses a series of simulation models of leprosy transmission and control with the objective of further clarifying mechanisms underlying the Norwegian time trend data. The following questions are addressed:

- Can the decline in leprosy be simulated?
- Can the age-shift in new case detection over time be explained?
- Can the contribution of isolation to the declining trend be assessed?

First, a statistical model is used, which does not include assumptions about leprosy or the fact that an infectious disease is addressed (curve fitting). Next, a simple standard infectious disease transmission model is applied which does not yet include age. These models only allow for exploration of the overall trend in new case detection. As a third step, models are introduced with an explicit age dimension in order to explain the shift in new case detection to older ages over time, as observed in Norway (*2*). Differences in contagiousness before and after onset of clinical symptoms of leprosy influence the degree to which isolation can prevent leprosy transmission. Various model variants are therefore considered which make different assumptions on the transmission of *Mycobacterium leprae* in successive stages of leprosy. The age-specific models are implemented in the SIMLEP framework for modelling the transmission and control of leprosy (*3*).

5.4 Material

History of leprosy and its control in Norway

A historical overview of leprosy research and control in Norway indicates that leprosy was not regarded as a serious health problem by the Norwegian authorities prior to the 1820s (*4*). Censuses of leprosy sufferers in 1836, 1845 and 1852 each time reported more new patients. Control measures were initiated following the 1852 census which reported 1782 patients. A Chief Medical Officer for Leprosy was appointed, and local measures were entrusted to District Health Officers. By Royal Decree in 1856, the National Leprosy Registry of Norway was founded. The first leprosy hospital in Norway, St. George's in Bergen, probably dates back to the 15th century. In 1849, a leprosy research hospital was completed. Three additional hospitals were built in the period 1854-1861. The total capacity in 1861 was 930 beds. In 1873, the leprosy bacillus *M. leprae* was discovered at the research hospital, and it became recognized that leprosy is an infectious disease. It was suggested that transmission could be reduced by isolation of contagious individuals from the general community. The admission to hospitals was voluntary up to 1875. By legislation acts of 1877 and 1885, leprosy patients either had to be isolated in separate rooms in their homes, or had to be admitted to a hospital, if necessary with the help of the police.

The National Leprosy Registry of Norway: patient data

The National Leprosy Registry was computerized in the 1970s, and consists of a district register and a hospital register. A detailed description of the database is available (*1*). The database includes information on birth, onset of disease as recalled by the patient, registration, admission to hospital, death, and emigration. Years of birth and onset of disease are available for 98% and 94% of patients, respectively. The year of detection refers to the first entry in either the district register or the hospital register. It is known for all registry patients. Nearly 60% of registry patients had at least one hospital admission recorded, and 72% of these admissions were permanent. We will use the term isolation to refer to the first hospital admission of a patient. For 96% of registry patients, the year of either death or emigration is available.

Trends in case detection

The registry contains information on 8231 patients, including 213 patients who were admitted to a hospital before the founding of the registry in 1856. The secular trend before 1856 is uncertain. Annual numbers of patients detected during 1856-1920 and corresponding case detection rates are given in Table 5.1. In 1856, many patients were detected (1796). This reflects the registration of a backlog of prevalent leprosy cases. The declining trend in new case detection rate accelerated over time and was on average about 7% per year during 1861-1920. Only 27 patients were detected after 1920.

Table 5.1 New leprosy case detection in Norway, 1856-1920.

Period	Population (personyears)	Number detected [a]	Detection rate per 100,000 personyears
1856-1860	7,671,135	2,833 [b]	36.9
1861-1865	8,199,131	1,146	14.0
1866-1870	8,597,373	1,034	12.0
1871-1875	8,828,299	797	9.0
1876-1880	9,326,248	692	7.4
1881-1885	9,620,933	428	4.4
1886-1890	9,859,632	358	3.6
1891-1900	20,958,385	411	2.0
1901-1910	23,095,413	220	1.0
1911-1920	24,997,694	72	0.3
Total		7,991	

[a] Out of the 8,231 registry patients, 213 were detected before 1856, and 27 after 1920.
[b] 1,796 cases were detected in the first year of the National Leprosy Registry, 1856.

Table 5.2 Age distribution of newly detected leprosy cases in Norway, 1856-1920.

Period	Contribution of age groups to total new case detection (%)						Total number detected
	0-14	15-24	25-34	35-44	45-59	60+	
1856-1860	5%	18%	26%	25%	12%	14%	2833
1861-1865	8%	21%	24%	20%	15%	13%	1146
1866-1875	8%	23%	24%	18%	16%	12%	1831
1876-1885	5%	21%	24%	18%	18%	13%	1120
1886-1900	6%	18%	20%	16%	18%	21%	769
1901-1920	3%	13%	18%	17%	19%	30%	292
Total	6%	20%	24%	21%	15%	15%	7991

The age distribution of cases detected during the period 1856-1920 is given in Table 5.2. The proportion of children is low. A shift towards older ages is observed after 1876: the percentage of newly detected cases of ages ≥ 35 increased steadily from 49% for 1876-1885 to 66% for 1901-1920. Demographic data show that the age structure of the Norwegian population hardly changed between 1856 and 1920 (5).

Times between onset, detection, isolation and emigration or death

Table 5.3 gives the mean times between onset and detection, between onset and isolation, emigration or death, and between onset and emigration or death (intervals 1-3). The longer intervals for patients with onset of disease before 1856 are due to length bias in

Table 5.3 Time from onset to events for leprosy patients, according to year of onset of disease, Norway, 1800-1920.

year of onset	number [a]	mean time (in years)		
		onset to detection (1)	onset to isolation, death or migration (2)	onset to death or emigration (3)
< 1851 [b]	1088	12.2	18.6	22.0
1851-1855 [b]	1201	3.8	9.4	12.9
1856-1860	1154	2.8	8.0	12.7
1861-1865	1009	2.7	7.3	11.8
1866-1870	996	2.8	7.0	11.7
1871-1875	716	3.2	6.9	12.3
1876-1885	865	3.2	6.4	12.1
1886-1900	551	3.5	6.1	11.9
1901-1920	160	3.2	6.2	13.0

[a] Concerns 7740 of the 8231 registry patients. For the remaining 491 patients, the year of onset was after 1920 for 14 patients, and not available for 477 patients.

[b] High values for mean times between events due to founding of registry in 1856, see text.

registration: apart from the 213 early hospital admissions, the registry only includes those patients that survived up to the founding of the registry in 1856. The delay in case detection (interval 1) was somewhat shorter in the first 15 years of the registry as compared to later years. Interval 2 gives an indication of the period during which symptomatic leprosy cases can transmit *M. leprae* under the assumptions that the first isolation is permanent, and that isolated patients stop contributing to transmission. The mean length of this period decreased initially due to an increase in the proportion of patients who were isolated, and was rather stable during 1876-1920. Since only 1% of the patients emigrated, the time between onset and emigration or death (interval 3) reflects the life expectancy at onset of leprosy. A clear trend is not visible. The additional time during which leprosy cases could transmit *M. leprae* when isolation would not affect transmission is reflected in the difference between the intervals 2 and 3, which is smaller in early as compared to later years (about 3.5 to 5 years between 1851-1870 versus about 6 years for 1876-1920).

5.5 Methods

Models

Three modelling approaches are used: statistical curve fitting, a transmission model without age-dimension and age-specific transmission models.

Statistical curve fitting

To fit the observed trend in case detection, a regression model that does not involve any assumptions about leprosy is used. Inspired by visual inspection, the log-transforms of the new case detection rates $D(t)$ with time t, $\ln(D(t))$, are fitted by a quadratic regression model, $\ln(D(t)) = \ln(D_0) - a \, (t - t_0)^2$, with three free parameters time t_0 (year in which the quadratic function starts to decline), D_0 (the detection rate at time t_0) and a (the strength of the quadratic decline in the log-transformed rates). This model is implemented in Excel.

Simple transmission model without age-dimension

The transmission model without age-dimension, shown in Figure 5.1, is also implemented in Excel. The in-flux of newborns in the SUSCEPTIBLE compartment is determined by a crude birth rate. Upon becoming infected, susceptible individuals move to ASYMPTOMATIC infection. A rate reflecting the length of the incubation period governs the transition from ASYMPTOMATIC infection to SYMPTOMATIC leprosy, i.e. the onset of clinical symptoms. The transition from SYMPTOMATIC to DETECTED reflects detection of leprosy. Detected patients who emigrate, die from leprosy or are isolated move to WITHDRAWN. The rates that describe the transitions to DETECTED and WITHDRAWN are referred to as 'registration rate' and 'withdrawal rate' respectively. All compartments are subject to death from other causes. Emigration rates as reported for the general population in Norway (5) are applied to the compartments SUSCEPTIBLE and ASYMPTOMATIC infection, which will contain most individuals.

Transmission is caused by individuals in the compartments SYMPTOMATIC and DETECTED. A transmission parameter represents the level of their contagiousness. Downward trends in leprosy can be the consequence of leprosy control, but may also have other causes, such as improvement of general living conditions. These autonomous factors are accounted for by assuming that the initial transmission parameter β_0 decreases by a constant annual reduction factor $\Delta\beta$ from a certain time t_0 onwards. The resulting transmission parameter $\beta(t)$ at time t beyond t_0 thus equals $\beta_0 (1 - \Delta\beta)^{t - t_0}$. The fraction of individuals in the SUSCEPTIBLE compartment that becomes infected in a time step Δt is calculated as $FOI \times \Delta t$, with force of infection FOI equal to $\beta(t) \, (SYM + DET) \, / \, N$ (SYM, DET = number of individuals in SYMPTOMATIC and DETECTED respectively; N = population size).

A policy of isolation causes detected individuals to move faster from DETECTED to WITHDRAWN. This results in lower forces of infection. Anti-leprosy treatment of patients is not considered because it only became available long after the end of the study period.

Age-specific models

An age-specific version of the simple transmission model with age-specific death rates and emigration rates is considered first (Model I). Starting from this model, a series of
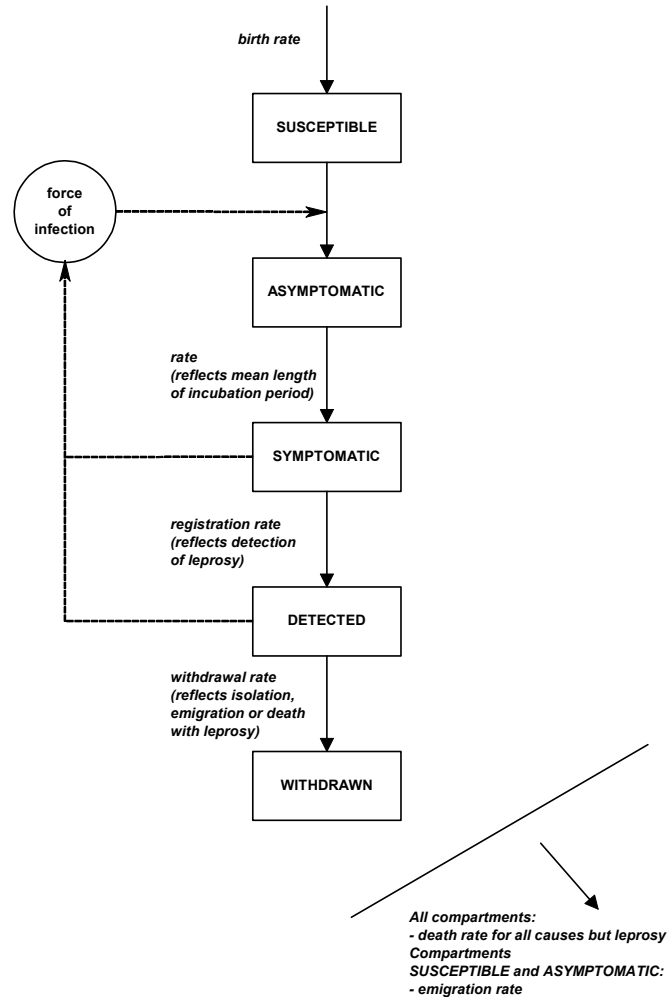
Figure 5.1 The transmission model.

models is explored. These models are implemented in the SIMLEP framework for modelling the transmission and control of leprosy, which was adapted to allow for emigration. SIMLEP uses a different time distribution for the duration of the incubation period to the simple transmission model (see below). A detailed description and discussion of the SIMLEP modelling framework has been provided before (*3*).

Directly estimated model parameters

Parameters of the simple transmission model and of the corresponding age-specific Model I are estimated as follows.

Birth, death and emigration

The birth rate and the crude and age-specific death rates for the middle decade 1881-1890 of the period 1851-1920 (*5*) are used in all simulations. The birth rate and crude death rate are 30.8 and 17.1 per 1000 population, respectively. The total and age-specific emigration rates vary over time and were derived from data that are available from 1836 onwards (*5, 6*).

Incubation period

The simple transmission model uses a constant transition rate based on a mean length of the incubation period of 11.0 years. The age-specific models use a time distribution with a mean duration of 8.6 years and less variation (five phase Erlang distribution (*3*)). The mean durations of the incubation period have been estimated from war veteran data (*7*).

Registration rates

These rates are derived from the observed mean times between onset of clinical symptoms and detection (Table 5.3: column 2), adjusted for death from all causes. The corresponding mean sojourn times in SYMPTOMATIC from the year 1857 onwards are given in Table 5.4 (the period before 1857 is addressed under 'Fitting the Norwegian leprosy trend data').

Withdrawal rates

The withdrawal rate *w* is based on the sojourn time distribution which minimizes the difference (using the Kolmogorov-Smirnov criterion) between:

(1) the distribution of the recorded times between onset and isolation, emigration or death, and

(2) the distribution of the total time in SYMPTOMATIC and DETECTED that results from subsequent application of the registration rate and this withdrawal rate *w* itself.

To investigate the impact of isolation, withdrawal rates are also estimated from the recorded times between onset and emigration or death only. All withdrawal rates are corrected for death from other causes. The corresponding sojourn times in DETECTED are given in Table 5.4.

Table 5.4 Mean sojourn times in the SYMPTOMATIC and DETECTED disease stages, according to year of onset of disease.

year of onset	mean sojourn time (in years)		
	in SYMPTOMATIC	in DETECTED: with isolation policy	in DETECTED: without isolation policy
1857-1860	2.9	3.8	10.1
1861-1870	2.9	2.9	10.2
1871-1875	from 2.9 to 3.5	from 2.9 to 1.7	from 10.2 to 9.0
1876-1920	3.5	1.7	9.0

Age-specific model: variants

Starting from Model I, variants involving assumptions about the following six aspects of transmission and of course of infection and disease (A1-A6) are explored.

A1 Geographic heterogeneity in exposure

In Norway, 98% of leprosy cases with onset between 1851 and 1920 originated from the counties in West and North Norway. The percentage of the Norwegian population living in these counties was stable at about 47% (*1*). Model I assumes homogeneous exposure of the susceptible population. The alternative assumption is that 53% of newborns will never be exposed to *M. leprae.*

A2 Genetic heterogeneity

Leprosy infection has been considered to be far more common than clinical leprosy (*7, 8*). The extent to which genetic factors influence the outcome of infection with *M. leprae* is as yet unknown (*9*). Model I assumes that every infection leads to clinical disease. The alternative assumptions are that 45% and 90% of individuals self-heal from infection without developing clinical disease. It is assumed that individuals who self-heal after becoming infected will not be re-infected and have immunity from ever developing clinical leprosy disease.

A3 Waning of transmission opportunities

Close contact to a leprosy patient, in their own household or through neighbours and social contacts, may be important for leprosy transmission. Since a contagious individual may infect close contacts rapidly, opportunities to transmit *M. leprae* may decrease with longer duration of disease. Model I neglects this possibility. In three alternative assumptions, it is assumed that the contribution of individuals with SYMPTOMATIC leprosy to transmission gradually decreases after onset of clinical symptoms, being halved every 2, 4 and 8 years, respectively.

A4 Build-up of contagiousness during ASYMPTOMATIC infection

Model I assumes that contagiousness of leprosy requires the presence of clinical symptoms, but this may not necessarily be true (*10*). The alternative assumption is that contagiousness builds up gradually from zero immediately after infection to the maximum level at onset of clinical symptoms.

A5 Age at maximum exposure

In Model I, exposure to *M. leprae* is assumed to be independent of age. SIMLEP offers the provision to specifying that exposure gradually increases from zero at birth to a maximum level from a certain age onwards. The alternative assumptions are that maximum exposure is reached at the ages of 1, 2,..., 10 years.

A6 Tail of the incubation period

The war veteran data on incubation periods involve small numbers of patients and only relate to adults becoming infected (*7*). The maximum time span available for diagnosis after leaving for service abroad was about 25 years for the vast majority of the veterans

(*11-13*). It has been suggested that manifestation of disease can be due to a mechanism similar to endogenous reactivation in tuberculosis (i.e. the manifestation is due to bacilli that were acquired earlier in life, and which persisted as dormant bacilli within the body) (*8*). This is not considered in Model I. The alternative assumption is that the distribution of the incubation period is a mix of a distribution with a mean of 8.5 years (as in Model I) and an essentially lifelong distribution (mean of 50 years) that expresses endogenous reactivation (two five-phase Erlang distributions).

Fitting the Norwegian leprosy trend data

All models are fitted to the Norwegian trend data. For each model, the values for the 'free' parameters are determined that minimize the difference between the observed and the estimated numbers of newly detected cases in successive time periods. The three free parameters for the quadratic model are *a, D_0* and *t_0*. The three free parameters for the transmission models are:

- β_0: the initial value of transmission parameter β,

- $\Delta\beta$: the annual proportional decrease in the transmission parameter which reflects 'autonomous decline' (i.e. secular decline due to factors other than isolation),

- t_0: the year in which the autonomous decline starts.

Age-specific models that involve assumption A6 have a fourth free parameter:

- the fraction of newly infected individuals with a mean of 50 years for the time distribution of the incubation period.

Simulations with the transmission models start in the year 1830 from a stable epidemiological situation, which is calculated on the basis of the model parameters (including the free parameter β_0). The decline in the simulated new case detection rates over time depends on changes in both registration and withdrawal rates (Table 5.4), and on the strength of the autonomous decline.

We quantify the free parameters of the quadratic model and the simple transmission model by fitting these models to the data on total new case detection from the period 1856-1920, using Excel's solver utility. The observed numbers of new cases O_i are given in Table 5.1. The model-generated new case detection rates are combined with the sizes of the Norwegian population for deriving the estimated numbers of newly detected cases E_i. The fit is evaluated as the weighted sum of the squared differences between observed and estimated numbers of cases for the nine time periods from 1861 onwards, (Table 5.1):

(1) $$D_1 = \sum_{i=1}^{9} (E_i - O_i)^2 / E_i$$

The age-specific Model I and variants with assumptions from A1 to A6 are quantified using the Nelder & Mead Simplex optimization method (*14*). Observed numbers $O_{i,j}$ of cases detected in time period *i* and age group *j* follow from Table 5.2 (five time periods,

six age groups). Estimated numbers $E_{i,j}$ again follow from simulated new case detection rates and Norwegian population data, and the weighted sum of the squared differences for evaluating age-specific models is calculated as:

$$(2) \qquad D_2 \;=\; \sum_{i=1}^{5} \sum_{j=1}^{6} (E_{i,j} \,-\, O_{i,j})^2 \;/\; E_{i,j}$$

First, Model I is fitted to the age-specific Norwegian trend data. Subsequently, a forward stepwise procedure is applied which with each step adds a new assumption from A1 to A6 to Model I. In each step, the assumption that is added is the one that gives the largest improvement in the goodness-of-fit score D_2. The stop criterion is a less than 10% improvement in D_2. The resulting model will be referred to as Model II.

The period before 1856

Case detection data before 1856 are very incomplete. The completeness of detection efforts in 1856 is not exactly known. Therefore, data from 1860 onwards are used to fit the models. We only marginally considered the early years, as follows. We assumed a detection delay of 12 years before 1856, and 90% detection of SYMPTOMATIC cases in 1856. Model quantifications are only rejected when the estimated and observed number of newly detected cases in 1856-1860 differ by more than 10%.

Impact of isolation

The impact of isolation is estimated using Model II by comparing the average annual decline d_{tot} as calculated from the simulated new case detection rates for 1861 and 1920, with results of a simulation which ignores the isolation policy by only using withdrawal rates that refer to emigration and death (Table 5.4). The average annual decline over 1861-1920 for this simulation, d_{sec}, is due to other factors than isolation (autonomous decline). The simulated contribution of isolation to the decline is estimated as $(d_{tot} - d_{sec}) \,/\, d_{tot}$.

In a sensitivity analysis of the impact of isolation, extensions to Model II are considered with assumptions from A1 to A6 that were not yet included due to the stop criterion in the forward stepwise procedure. Only those assumptions are selected for which the goodness-of-fit score D_2 of Model II does not decrease by more than 10%. The impact of isolation is also determined for these variants.

5.6 Results

Trend in total new case detection

The new case detection data of Table 5.1 are more or less equally well fitted by the quadratic model, the simple transmission model and the corresponding age-specific version (Model I). The goodness-of-fit scores equal 17, 17 and 22, respectively

Table 5.5 Start of autonomous decline and goodness-of-fit score for the fit of different model variants against Norwegian leprosy new case detection data, 1856-1920.

Model [a]	Start of autonomous decline	Goodness of fit score
evaluation: trend in total new case detection		
Quadratic regression model	n.a.	17
Simple transmission model	1863	17
Model I	1868	22
evaluation: age-specific trend in new case detection		
Model I	1861	204
Model I + A5 [b]	1866	104
Model I + A5 + A6	1867	79
Model I + A2 + A5 + A6 [c]	1866	66
Model II = Model I + A1 + A2 + A5 + A6	1865	60

[a] A1: Geographic heterogeneity in exposure; A2: Genetic heterogeneity; A5: Age at maximum exposure; A6: Tail of the incubation period.
[b] With age at which maximum exposure is reached: 4 years (A5).
[c] With percentage of new infections that self-heal without manifestation of clinical disease: 90% (A2).

(Table 5.5). Statistically significant differences ($p < 0.05$) between data and model results are observed for the consecutive periods 1876-1880 (estimates lower than data) and 1881-1885 (estimates higher than data). The less good fit for Model I is entirely attributable to these two periods. For the decade 1876-1885 as a whole, estimated total new case detection deviates by less than 1% from the Norwegian data for all three models.

The decline in new case detection rate in Norway accelerated over time. The quadratic model estimates an increase in decline from 4.5% during 1861-1880 to 9.2% during 1901-1920 (Figure 5.2). The simple transmission model and the age-specific Model I estimate that both the overall decline and the autonomous decline in transmission started in the 1860s. The fit of the age-specific Model I worsens considerably when the start of the autonomous decline is postulated to occur before 1855.

Age-specific trend in new case detection

The fit of Model I to the age-specific Norwegian trend data from Table 5.2 is poor. Too many child cases are estimated for all time periods considered, and also too few cases of ages ≥ 60 for 1896-1900 and 1901-1920. The reason for the latter finding is that Model I fails to reproduce the observed shift in new case detection towards older ages: the estimated percentage of new cases of ages ≥ 35 only increases by 2% between 1876-1885 and 1901-1920 (Model I: 48% versus 50%; data: 49% versus 66%). The child case group
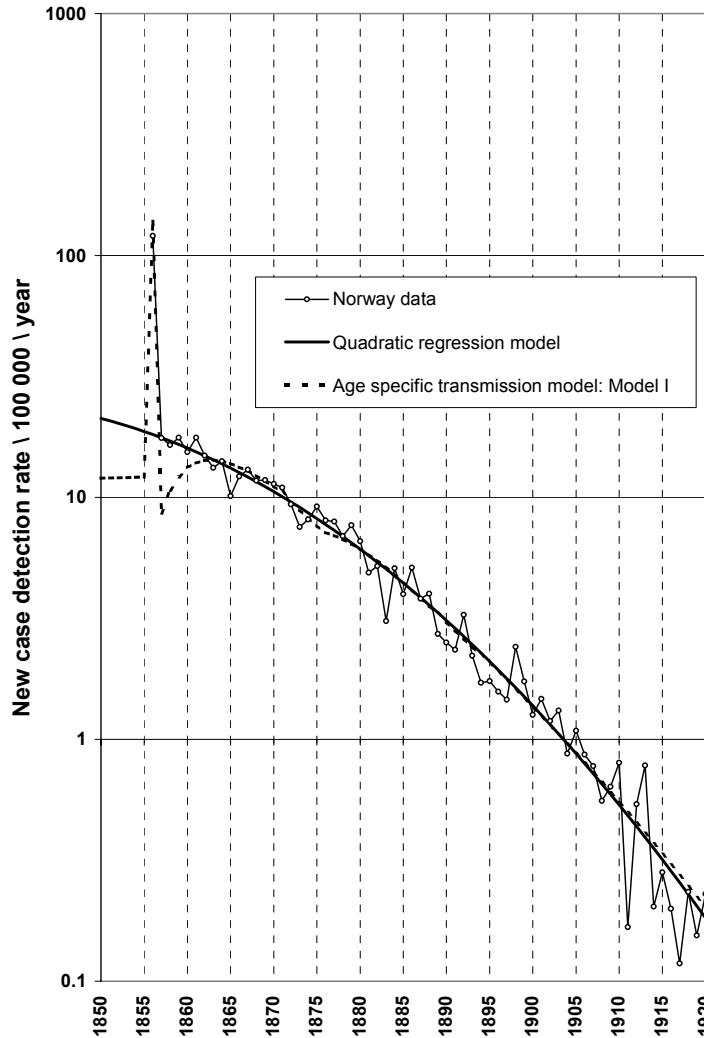
Figure 5.2 Trend in total new case detection rate: comparison between observed data and estimates by the quadratic regression model for log-transformed new case detection and by the first age-specific transmission model (Model I), Norway, 1856-1920.

and the failure to reproduce the age shift together account for more than 60% of the goodness-of-fit score of Model I, which equals 204 (Table 5.5).

The largest improvement of the fit is obtained by extending Model I with assumption A5: the goodness-of-fit score halves by assuming that maximum exposure is reached at age 4, due to much better estimates for the child case group (Model I + A5). First adding

assumption A6 also leads to a major improvement: assuming a long tail for the distribution of the incubation period results in a satisfactory reproduction of the age shift and a goodness-of-fit score of 145 (Model I + A6).

Table 5.5 shows that stepwise extension of Model I with A5 and A6 reduces the goodness-of-fit score to 79. By adding the assumptions A2 (genetic heterogeneity with 90% self-healing infections) and A1 (geographic heterogeneity in exposure) in the next two steps, the score further improves to 60. The resulting model is denoted as Model II (= Model I + A1 + A2 + A5 + A6). The fitting results for Model II are as follows: the autonomous decline in transmission starts in 1865, and 9.7% of newly infected individuals have a long incubation period (mean duration of 50 years) which causes ages at detection to increase with time. No substantial further improvement is achieved by adding the remaining assumptions A3 and A4.

Table 5.6 and Figure 5.3 compare age-specific new case detection as simulated by Model II with the observed Norwegian data. No important systematic under- or overestimation of child cases (ages 0-14) occurs. The shift in new case detection towards older ages over time is reproduced well: the estimated percentage of new cases of ages ≥ 35 increases from 50% for 1876-1885 to 65% for 1901-1920 (data: 49% to 66%). Statistically significant differences between estimated and observed numbers of newly detected cases are observed in 4 out of the 30 cells of Table 5.6. These differences are largely due to fluctuations in observed new case detection rates with age which are not well understood: from 1861 to 1885, the rates were highest for the age group 25-34, and lower for the age group 45-59 than for those of ages ≥ 60 (Figure 5.3). These fluctuations are also largely responsible for the difference in the age-specific fits of Model II itself and the earlier Model I + A5 + A6 which includes the two assumptions that influence the goodness-of-fit most. The importance of this difference is not clear, and some caution in the comparative judgement of these two models is indicated.

Table 5.6 Age-specific new case detection: comparison between estimates by the age-specific Model II and observed data, Norway, 1861-1920.

Period	New case detection: difference (%) between estimated (E) and observed (O) numbers by age [a]					
	0-14	15-24	25-34	35-44	45-59	60+
1861-1865	17%	11%	-11%	-13%	4%	-8%
1866-1875	2%	8%	-13%[b]	-4%	15%[c]	0%
1876-1885	13%	7%	-13%[b]	-14%	12%	7%
1886-1900	-34%[b]	1%	0%	4%	12%	-11%
1901-1920	27%	18%	-9%	-14%	16%	-9%

[a] Differences calculated as *(E-O) / E*.
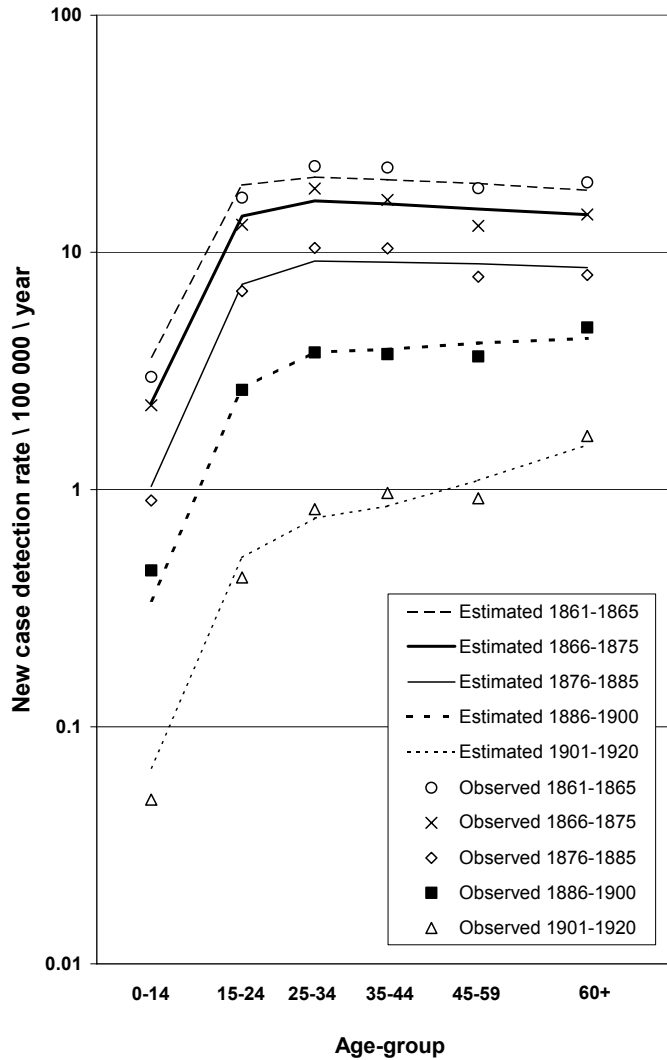[b] *p* < 0.05.
[c] *p* < 0.01.

Figure 5.3 Trend in age-specific new case detection rate: comparison between observed data and estimates by the age-specific Model II.

Role of isolation

The contribution of isolation to the simulated decline in new case detection rate over 1861-1920 is 60% for Model II, and 68% for the earlier Model I + A5 + A6 which excludes geographic and genetic heterogeneity. Seven new models result from extending Model II with the remaining assumptions regarding waning of transmission opportunities (A3) and build-up of contagiousness during the incubation period (A4) (Table 5.7). Since

Table 5.7 Sensitivity analysis: estimated contribution of isolation to the total decline in new case detection rate for Model II and variants of Model II, Norway, 1861-1920.

Half-value time for transmission opportunities [a]	Contribution of isolation to decline	
	Build-up [b]: no	Build-up [b]: yes
infinite [c]	60% [d]	36%
8 years	39%	17%
4 years	27%	9%
2 years	14%	3%

[a] Reflects waning of transmission opportunities due to rapid transmission to close contacts (A3).
[b] Build-up of contagiousness during ASYMPTOMATIC infection: yes or no (A4).
[c] No waning of transmission opportunities.
[d] Estimated contribution of isolation for Model II.

the fits do not worsen by more than 10%, these new models are all included in the sensitivity analysis for investigating the role of isolation. Table 5.7 shows that the contribution of isolation strongly depends on the precise assumptions made: it varies between almost no impact (3%) and 39% (Model II: 60%). The contribution decreases with more rapid waning of transmission opportunities (A3) and/or with build-up of contagiousness during the incubation period (A4). This is not surprising because less transmission can be prevented through isolation under these assumptions, which necessitates a stronger autonomous decline that starts earlier in order to arrive at good fits of the data. The start of the autonomous decline varies from 1846 to 1857 for the seven new models (Model II: 1865).

5.7 Discussion

The disappearance of leprosy in Norway has been analysed by epidemiological models that explain both the time trend in total new case detection and the shift towards older ages. Various model variants are capable of explaining the data, but the estimated impact of isolation varies widely between these variants.

Reproduction of the Norwegian trend data

The quadratic regression model fits the accelerating decline in total new case detection well but it does not provide insight into the mechanisms (including the isolation policy) which may have governed the declining leprosy trend. A simple transmission model also produces this acceleration. Its age-specific version has two problems: too many child cases are predicted, and the shift in new case detection towards older age groups is missed.

The problem with detection rates in children is solved by letting the exposure to *M. leprae* gradually increase from zero at birth to a maximum level that is reached in young childhood. We are aware that this assumption is rather arbitrary. International data on age-specific new case detection rates vary. Peaks in the age group 10-20 have been observed several times (*7*). A study from Bangladesh shows a peak in the new case detection rate for ages 10-14 in females, while rates continue to rise in males until age 25 (*15*). In Norway, new case detection rates are highest for the age group 25-34 during the first few decades of the study period (Figure 5.3). Causes that may underlie this variation include the role of intra-household transmission and the duration of the incubation period which appears to be related to the type of leprosy (*7*) (the frequency of lepromatous leprosy was always high in Norway (*1*)). In addition, the extent of natural immunity, factors related to gender, endemicity levels of leprosy, and operational factors (case detection methods) may be relevant.

Different explanations are possible for the observed shift in new case detection towards older age groups. Firstly, detection may have been delayed longer, however, no important increase in the detection delay was found in the registry data. Secondly, case detection at older ages is limited by the decreasing number of remaining susceptibles when transmission is high. A decrease in transmission will lead to an increase in the number of susceptibles at older ages, and thus to an increase in infection rate at older ages. However, leprosy transmission was quite low even at the start of the study period, and the susceptibles constitute the largest part of the population throughout the study period.

The third explanation relates to the incubation period. The fraction of new cases with long incubation periods will increase over time with decreasing transmission levels, which will cause ages at detection to go up. The variance in the time distribution of the incubation period should be sufficiently large to reproduce the observed age shift. We reproduce this age shift by adding a long tail to the baseline incubation time distribution (Figure 5.3). According to this distribution, 7% of all incubating individuals has an incubation period of at least 25 years. This percentage is still compatible with further analyses of the war veteran study which showed that the follow-up period did not exceed 25 years for the vast majority of the war veterans (*7, 11-13*). The long incubation periods are consistent with the suggestion that reactivation of bacilli that were acquired earlier in life, and which persisted as dormant bacilli within the body (endogenous reactivation) may play a role in the manifestation of leprosy disease (*8*).

Due to the transmission cycle, detected numbers of cases in subsequent time periods are interdependent. In addition, sizeable fluctuations in observed numbers of detected cases occur over time and with age which are difficult to explain. Therefore, we considered a formal χ^2 test overkill, and restricted ourselves to comparative analysis of the various models and their fits. The SIMLEP model framework which has been used for the age-specific models is limited in possibilities for varying model assumptions. More freedom to vary model parameters could potentially result in much lower values of the age-specific goodness-of-fit score.

Role of the isolation policy

The isolation regime in Norway was relatively mild: hospital patients had full freedom of movement, but had to spend the night in hospital (*4*). An earlier epidemiological analysis showed that the *degree of isolation*, a measure reflecting how often and long patients were hospitalized, was associated with relative falls in leprosy incidence rates between subsequent decades in different counties (*1*). Both the degree of isolation and the decline in incidence rate increased over time.

Our study shows that the model variants that are compatible with the observed age-specific trend data lead to a broad range of estimates for the contribution of isolation to the decline (from 3% to 60%). The impossibility of measuring contagiousness is an important cause of this broad range. The estimated contribution of isolation to the decline was lower when much of the transmission was assumed to occur before the onset of symptoms. Discussions are ongoing on who is responsible for leprosy transmission. Cree *et al* (*10*) suggest that infection from 'subclinical sources' may be more important than infection from symptomatic cases. There is even evidence from Norway and from other countries suggesting existence of environmental sources of infection in addition to human sources (*16, 17*).

The estimate for the role of isolation also became lower when transmission opportunities were assumed to wane during the infectious period. Whether and to what extent waning really occurs is not known. It is more likely to occur if close contact to a patient is important for the transmission of leprosy. Family clustering of patients was observed in Norway despite of incomplete information (*1*). By also considering neighbour and social contacts, a recent study of an Indonesian village showed that close contact may be more important for transmission than is commonly believed: out of 101 cases newly detected over a period of 25 years, 78% could be associated to other patients (household contact: 28%, neighbours and neighbours of neighbours: 36%, social contacts: 15%) (*18*). The suggestion that many individuals who become infected with leprosy do not develop clinical leprosy disease (*7, 8*) further supports hypothesising waning of transmission opportunities.

The model from which the sensitivity analysis for the role of isolation started, Model II, assumes geographic and genetic heterogeneity. The estimated contribution of isolation to the decline was somewhat higher when these heterogeneities were ignored (68% versus 60%). In endemic areas, individuals not developing leprosy through endogenous reactivation may well have shorter incubation periods than the war veteran data (*7*) suggest. Shorter incubation periods reduce the turnaround time of the transmission cycle, thus increasing the estimated impact of isolation on reported trends. The estimated contribution of isolation indeed increases from 60% to 67%, when a mean duration of 6 instead of 8.5 years is used for the incubation period in Model II (a similar fit is realized, and the long tail is maintained). Smaller means resulted in too rapid declines in new case detection rate in the first few decades of the study period.

More complex models could be considered. For instance, we do not distinguish between different types of leprosy disease. Also, we do not take gender differences into account. Undoubtedly, adding complexity would lead to other estimates of the contribution of isolation to the decline. However, such additions would not tackle the problem of measuring contagiousness, and the uncertainty regarding the role of isolation will remain. Therefore, further complexity would not add to the insights gained through the present analysis.

Other contributing factors

We represented the way transmission may be influenced over time by factors other than isolation simply by a constant annual reduction factor. The earlier epidemiological study identifies several such factors (*1*). These include nutritional conditions, a rise in tuberculosis, and selective emigration to overseas countries. At farm level, the occurrence of leprosy is shown to be associated with a low production of oats and milk. No doubt, nutritional conditions greatly improved during the second half of the 19th century (*1*). This is in line with a historical analysis of the Norwegian economy by Bergh *et al* which shows growth in the production per capita from 1830 onwards after centuries of economic stagnation (*19*). This growth continued virtually without interruption for the next 150 years. Thus, the Norwegian population may, due to improved nutritional conditions, have been rendered more resistant to infections with *M. leprae* (*1*), which may have originated from environmental sources (*16*). Morbidity rates of tuberculosis, which may protect against leprosy (*7*), either by immunization or by competing risk, increased in Norway until beyond the turn of the 19th century (*1*). The increase was relatively high in the coastal counties (leprosy was particularly frequent in the coastal counties). Emigration heavily influenced the Norwegian demography (*20*). It was particularly frequent in areas, and in age and sex groups, with high leprosy incidence rates. The assumptions made on emigration in this study hardly affect estimated impacts of isolation. We could, however, not exclude whether *selective* emigration would affect estimates on the impact of isolation.

Relevance for contemporary leprosy control

The estimated impact of isolation strongly depends on assumptions made about leprosy transmission. The results also have a modern interpretation, because both isolation and anti-leprosy treatment of patients, which became available long after leprosy had disappeared from Norway, prevent leprosy transmission. Nowadays, early case detection followed by chemotherapy treatment (multidrug therapy: MDT) forms the mainstay of leprosy control. It is unclear to what extent present-day control influences leprosy trends in populations. Currently, we are performing a model-based scenario analysis to predict plausible leprosy trends up to 2020 and the influence of present day control. The scenario predictions are complicated by the same factors that we encountered in the evaluation of the decline of leprosy in Norway. A logical next step in our approach would be a model-based analysis of long-term trends in geographical areas with comparable general conditions, but with different well-documented leprosy control policies. Such data would

enable further clarification of the forces driving leprosy trends, but are unfortunately not readily available. Epidemiological studies which apply modern diagnostics and address different hypotheses on leprosy transmission (e.g. (*10, 17, 18*)) may improve knowledge on leprosy transmission. Further development, testing and application of various diagnostic tools is required, including serological tests and tests using skin reagents for detection of subclinical and early clinical leprosy, DNA amplification for detection of carriage of *M. leprae* in nasal swabs, and DNA fingerprinting to distinguish between different strains of *M. leprae.* Improved knowledge about the contagiousness of individuals and the process of leprosy transmission would greatly improve the conditions for evaluation of the impact of interventions such as early case finding in combination with chemotherapy treatment, vaccination strategies, and chemoprophylaxis of close contacts of leprosy patients.

5.8 Key messages

- Between 1850 and 1920, leprosy disappeared from Norway.

- The extent to which the Norwegian policy of isolation of leprosy patients has contributed to the decline through interruption of the transmission of leprosy is uncertain.

- Estimates of the impact of isolation depend strongly on assumptions about occurrence of transmission during the incubation period and about the importance of close contacts in transmission.

- Evaluation of contemporary leprosy control through chemotherapy is confronted with the same uncertainties about leprosy transmission.

5.9 Acknowledgment

5.10 References

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6

The future incidence of leprosy:
a scenario analysis

6.1 Summary

Objective To investigate the impact of the current strategy for the elimination of leprosy on its incidence and to assess the consequences of failure to sustain this strategy.

Methods Scenarios for assessing the impact of the elimination strategy were implemented in a computer simulation program. The scenarios reflected the assumptions made regarding contagiousness, transmission and bacille Calmette-Guèrin (BCG) vaccination. The trend in case detection rate for the main countries in which leprosy was endemic during 1985-1998 was fitted, and incidence up to 2020 was projected.

Findings Owing to the gradual shortening of delays in detection up to 1998, and because of the low relapse rate that occurs with multi-drug treatment (MDT), incidence is predicted to decrease beyond 2000 in all scenarios. The annual decline was a few per cent higher when favourable assumptions were made about protection and coverage of BCG vaccination. Overall, the predicted annual decline in incidence rates ranged from 2% to 12%.

Conclusion The elimination strategy reduces transmission, but the decline may be slow. Relaxation of control after 2005 is unjustified given the uncertainty about the rate of decline and the adverse effects of longer delays in detection. A long-term strategy for leprosy control should be adopted.

6.2 Keywords

Leprosy / Elimination; Early detection; Chemotherapy; BCG vaccination; Computer simulation

6.3 Introduction

The mainstay of current leprosy control is early detection and treatment with MDT. The number of patients receiving treatment declined after implementation of MDT because the period of treatment for MDT is shorter than that for dapsone monotherapy. At the same time, the annual number of new leprosy cases increased (*1*). These contrasting trends result from changes in control programmes, and the impact of MDT-based control on transmission is unknown.

MDT was introduced in 1982 because of the emergence of resistance to dapsone monotherapy (*2*). Relapse rates are low (*3*). MDT has improved the image of leprosy as a curable disease and has led to increases in the commitment of national health services to finding and treating leprosy patients (*4, 5*). In 1991 optimism about the impact of MDT led the World Health Assembly (WHA) to pass a resolution to "eliminate leprosy as a public health problem" by the year 2000. This elimination target led to intensive case-finding campaigns, called "leprosy elimination campaigns" in the late 1990s. The WHA resolution has therefore indirectly caused the increase in global case detection.

The elimination target was defined as a prevalence of less than one person per 10 000 population registered for treatment by the year 2000 (*6-8*). During this year, the number of patients registered for treatment worldwide fell below the target level (*9*). This achievement was largely the result of two operational factors: the duration of treatment was shortened, and patients not in need of treatment, but possibly with disabilities, were removed from registries (*10, 11*). This elimination target differs from the concept of "elimination of an infectious disease", which is defined as the absence of incident cases in a defined geographic area (*12*).

In order to reach the elimination target in all countries by the end of 2005, the World Health Organization (WHO) formulated a strategy based on early case detection and MDT, called "the Final Push" (*13*). This strategy is intended to "reduce the leprosy burden to very low levels, and therefore liberate resources to address other health priorities in the community". In response, the editor of *Leprosy Review* pointed out that there is no evidence that reaching the target will reduce transmission, and expressed serious concerns regarding the fulfilment of future demands to control leprosy (*11*).

An assumption underlying the elimination strategy is that MDT will reduce transmission through reduction of the number of contagious individuals in the community, but evidence to support this assumption is lacking (*14-16*). Data to evaluate the impact of MDT are not readily available, for several reasons. Because leprosy has a long and variable incubation period (*17*), decreases in transmission only gradually become evident. Also, declines in case detection may have other causes, such as BCG vaccination. BCG vaccination is used against tuberculosis, but appears to afford greater protection against leprosy (*18*). Variability in control efforts further complicates the interpretation of trend data.

How much transmission a control strategy can prevent depends on two unresolved issues. Is the incubation period contagious, and, are close contacts of a patient infected rapidly? In this article, we describe scenarios based on certain assumptions regarding earliness of case detection, the above-mentioned unresolved issues and BCG vaccination. These scenarios were explored using the epidemiological modelling framework known as SIMLEP which was designed for assessing and predicting trends in leprosy (*19*). For each scenario, the trends in incidence and case detection up to 2020 were projected. By comparing the projections, the impact of the current MDT-based elimination strategy could be explored. An analysis of the sensitivity of the projections for uncertainties in leprosy epidemiology was undertaken. Finally, the consequences of relaxation of the elimination strategy beyond 2005 were predicted.

6.4 Methods

SIMLEP distinguishes states to describe the course of leprosy infection and disease. Changes in these states are determined by epidemiological parameters. The parameter values and a set of mathematical equations determine how an epidemiological situation, i.e. the proportions of the total population within the various states, evolves over time.

Different models can be specified within SIMLEP. The essential features of the model used in this study are as follows. The number of births is based on a birth rate applied to the general population. Newborns are susceptible to leprosy and susceptible individuals can become infected as a result of transmission. New infections self-heal, or progress either to contagious disease which does not self-heal, or to non-contagious disease which self-heals, i.e. the patient becomes free from bacteria. Self-healing is a well-recognized phenomenon (*17, 20, 21*). The appearance of the first clinical symptom denotes the onset of disease, or incidence. A transmission parameter reflects the contagiousness of individuals with contagious disease. SIMLEP considers two interventions: (early) case detection followed by chemotherapy, and BCG vaccination, with the associated states "on treatment" and "vaccinated", respectively. The time between onset of disease and case detection, or detection delay, reflects the length of time for which an individual with contagious disease can transmit *Mycobacterium leprae*, and can be varied in SIMLEP. Further assumptions regarding transmission and interventions are varied in the scenario analysis, see below. SIMLEP is age-specific. A life table governs mortality.

The appendix gives more details on the model used including a graphical representation, and provides the quantification of the parameters. A detailed description of SIMLEP is provided elsewhere (*19*). SIMLEP is conceptually similar to models for tuberculosis (*22, 23*).

Transmission of leprosy

Two gaps in knowledge were found to be critical in a SIMLEP-based investigation of the role of control in the disappearance of leprosy from Norway (*24*).

Does contagiousness build up during the incubation period of leprosy? Contagiousness does not necessarily require the presence of clinical symptoms. We consider two possibilities; the first is that there is no contagiousness during the incubation period, and the second, that there is gradual build-up of contagiousness during the incubation period. The level of contagiousness is assumed to be constant after onset of disease.

Do opportunities to transmit M. leprae decrease over time? Because close contacts, who are the people most at risk, may be infected rapidly, the opportunities to transmit *M. leprae* may decrease over time. In addition to no decrease, we considered half-value times for transmission opportunities of 2, 4 and 8 years. The decrease starts at onset of disease.

Leprosy control

The value assigned to the detection delay reflects earliness of case detection. In SIMLEP, chemotherapy is considered to start immediately following case detection, and to stop contagiousness instantaneously, because both dapsone and MDT render patients non-contagious quickly (*25*). In the scenario analysis, dapsone is used from the start of the simulations in 1960, and MDT from 1990 onwards. The main differences between dapsone and MDT are the duration of treatment and the risk of relapse after treatment.

Trends in the detection delay were based on information recalled by patients from areas with good control (*26-31*). Our assumptions are as follows. The average detection delay gradually decreased from an initial period of 12 years (no control) to 6 years in 1990, reflecting the gradual establishment of control programmes. Subsequently, the average delay decreased to a constant 4 years for 1992-1996, corresponding to intensified control after the 1991 WHA resolution (*32*). Next, following the initiation of leprosy elimination campaigns (*33*), the average delay decreased further to 2 years in 1998. For the future, we considered two possibilities. The first is that the delay remains constant until 2020. The second is that the average delay gradually increases from 2 to 4 years between 2006 and 2009, and remains constant thereafter reflecting failure to sustain early case detection.

The protective efficacy of BCG against leprosy is well established, although the reported efficacy varies widely (*18*). The policy in most developing countries is to vaccinate only very young children (*34*). Country data on immunization coverage are disseminated by WHO (*35*). We consider two policies: no vaccination at all, and, vaccination of infants starting in 1975 with an initial coverage of 5%, increasing to 80% in 1990, and to 95% in 1999 and later years. In SIMLEP, BCG reduces the chance of an individual becoming infected. A non-waning protective efficacy of 50% was assumed.

Scenarios: procedure

The alternative assumptions regarding contagiousness during incubation of disease, waning of transmission opportunities and BCG vaccination resulted in 16 (2×4×2) scenarios: eight without BCG and eight with BCG. Each scenario was fitted to a reference case detection rate (CDR) during 1985-1998. The CDR trends since 1985 are described elsewhere (*1*) using reported information (*36-42*). Reference CDRs are

calculated as the average of the CDRs of the countries that satisfied two criteria, namely that at least 2000 cases were detected in 1998, and that figures on the number of cases detected had been reported throughout 1985-1995. Fourteen countries satisfied these criteria: Bangladesh, Brazil, China, Ethiopia, Guinea, India, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Philippines, Sudan and Viet Nam. The reference CDR increased from 1.3 per 10 000 total population per year in 1985 to 2.3 per 10 000 in 1998, which corresponds to an average annual increase of 4.6% (Figure 6.1). The increase was the result of the intensification of control following the WHA elimination resolution, and of leprosy elimination campaigns.

In the scenario simulations, the postulated reductions in the detection delay may first induce increases in CDR (see Results). On the other hand, these reductions imply that contagious cases are detected earlier and earlier. This may bring about reductions in transmission, and after a time lag due to the incubation period and detection delay, also to reductions in incidence and CDR.

The reference trend is fitted by varying SIMLEP's transmission parameter for the level of contagiousness of individuals with contagious disease (*19*). The best fit of a scenario is obtained by minimizing the sum of the squared differences between the simulated CDR and reference CDR between 1985 and 1998. After fitting, projections of the incidence rate and CDR until 2020 were made (see above).

Sensitivity analysis: procedure

Leprosy epidemiology is fraught with uncertainty, and a sensitivity analysis was carried out to account for this. The following seven parameters are varied one by one: percentage of infected individuals who do not develop disease, duration of the incubation period, percentage of new cases who develop contagious disease, self-healing rate for non-contagious self-healing disease, trend in detection delay, duration of dapsone monotherapy and relapse rate after dapsone.

For each new parameter value, the eight scenarios with BCG were again fitted to the CDR reference trend. Projections are made under the assumption that early case-finding and treatment are sustained until 2020 (i.e. a constant detection delay of 2 years is used). Results were compared with those obtained with the baseline assumptions. Tables 6A.2 and 6A.3 in the appendix specify the parameter values used in the sensitivity analysis.

6.5 Results

Scenarios without BCG vaccination

Figure 6.1a shows the simulated CDR and the incidence rate for the scenario in which leprosy is most difficult to control; i.e. the disease is contagious during the incubation period and opportunities for transmission wane fast. The simulated CDR roughly follows the reference data, suggesting that the trend in the observed seemingly capricious CDR
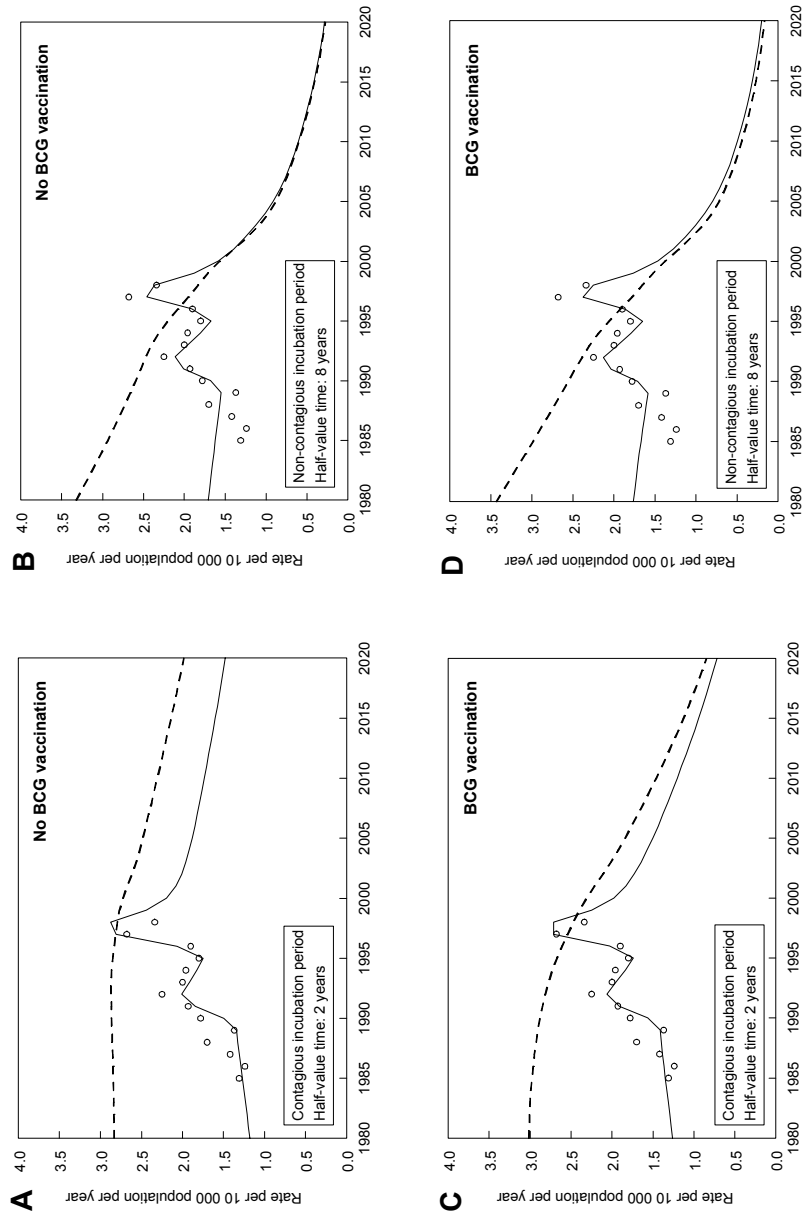
Figure 6.1 Trends in incidence rate and case detection rate. The circles display the case detection reference data, and the solid lines give projected case detection rates. The dashed lines give the projected incidence rates. Figures 6.1a and 6.1c differ from Figures 6.1b and 6.1d in the assumptions made about contagiousness of leprosy and waning of transmission opportunities. Results are given both with (6.1c, 6.1d) and without (6.1a, 6.1b) BCG vaccination.

can be explained by reductions in detection delays. These reductions were associated with the removal of backlogs in case detection and ceased in 1998, which explains the peak and subsequent drop in simulated CDR. The simulated CDR then started to follow the trend in the incidence rate because the detection delay was not reduced further. Relative to the incidence rate, the simulated CDR beyond 2000 was higher than in the 1980s because fewer patients with non-contagious leprosy self-healed before detection. The incidence rate was constant until 1995, and the average decrease in incidence rate predicted between 2000 and 2020 is 1.6% per year.

Figure 6.1b depicts a scenario in which leprosy is easier to control; i.e. there is no transmission during the incubation period and transmission opportunities wane slowly. Before 1990, the incidence had already decreased. Nevertheless, the simulated CDR again increased in the 1990s due to the reductions in detection delays. The trend in the incidence rate determines the trend in simulated CDR beyond 2000, as in the previous scenario. The projected average annual decline in incidence rate during 2000-2020 is 8.3%.

In six of the eight scenarios without BCG, the CDR increased during 1985-1998, with a difference from the 4.6% annual increase in the reference trend of less than 50% (Table 6.1). These increases coincided with incidence rates in the same period which were either stable, or decreased by up to 3.6% annually. As expected, the decline in incidence rate beyond 2000 is faster when the incubation period is not contagious, and when the transmission opportunities wane more slowly. The projected decline in incidence rate accelerates after 2000 in all scenarios because detection delays became shorter in the 1990s, but also because few relapses occur after MDT. For the six scenarios, the average annual decline in incidence rate projected for 2000-2020 ranges from 1.6% to 8.3% (corresponding range for the time needed to halve the incidence rate: from 8 to 43 years). The two remaining scenarios assumed that transmission opportunities do not wane over time and show a stable CDR (annual changes: between –1% and 1%), which conflicts with the reference trend.

Scenarios with BCG vaccination

The addition of BCG vaccination had a small impact up to 2000, because only infants are vaccinated and coverages were initially low. Therefore, no important changes were noted in the fit of the reference trend and in the decline in incidence rate during the reference period 1985-1998 (Table 6.1). BCG vaccination is projected to enhance the annual decline in incidence rate during 2000-2020 by a few per cent, with a resulting range for the annual decline in incidence rate from 4.9% to 10.0% for the six scenarios with a good fit. The time required to halve the incidence rate varies from 7 to 14 years. The scenarios with the least and most favourable projections (see Figures 6.1c and 6.1d), have 57% and 39% lower incidence rates in 2020 than in the corresponding scenarios without BCG.

Table 6.1 Trend in case detection rate (CDR) and in incidence rate for the 16 scenarios. The scenarios with trends indicated in bold are the subject of Figure 6.1. [a]

Incubation period contagious?		Yes				No			
Half-value time of transmission opportunities (years):		No [b]	8	4	2	No [b]	8	4	2
Without BCG vaccination	Fit of trend in case detection rate: 1985-1998	Poor	Good	Good	**Good**	Poor	**Good**	Good	Good
	Annual decrease in incidence rate: 1985-1998	5.5%	2.4%	1.1%	**0.1%**	6.4%	**3.6%**	2.0%	0.5%
	Annual decrease in incidence rate: 2000-2020	8.9%	5.2%	3.3%	**1.6%**	10.6%	**8.3%**	6.6%	4.3%
With BCG vaccination	Fit of trend in case detection rate: 1985-1998	Poor	Good	Good	**Good**	Poor	**Good**	Good	Good
	Annual decrease in incidence rate: 1985-1998	6.5%	3.5%	2.3%	**1.4%**	7.2%	**4.4%**	3.0%	1.5%
	Annual decrease in incidence rate: 2000-2020	10.9%	7.9%	6.3%	**4.9%**	11.9%	**10.0%**	8.5%	6.5%

[a] A trend in CDR between 1985 and 1998 is scored as Good when the scenario has a CDR increase that differs at most by 50% from the 4.6% annual increase in the CDR reference data (i.e. between 2.3% and 6.9%), and is otherwise scored as Poor. The four scenarios in which no waning of transmission opportunities occurs show either no increase in CDR or an average annual increase below 2.3%.

[b] Transmission opportunities do not decrease over time.

Scenarios without sustained early case detection and treatment

The consequences of an increase in the detection delay after 2005 are shown in Figures 6.2a and 6.2b. Initially, the CDR decreases considerably because detection is postponed and more self-healing cases will go undetected. However, the prolonged delay also implies increased transmission which, after some delay due to the incubation period, results in a slower decrease of the incidence rate. The consequences of failure to sustain early case detection are similar for the other scenarios.

Sensitivity analysis

Of the seven parameters varied in the sensitivity analysis (see appendix: Table 6A.3), only two – the length of the incubation period and the trend in detection delay – led to a substantial change in the annual decline in incidence rate beyond 2000. In all other cases, the annual declines are very close to the baseline value (maximum difference, 1%).

Halving the length of the incubation period leads to a faster decrease in the incidence rate because shorter incubation periods imply shorter transmission cycles. The effect is greater for the unfavourable scenarios; the decline in incidence rate beyond 2000 is up to 4% higher. Of the four scenarios with a good fit to the reference trend, the highest annual
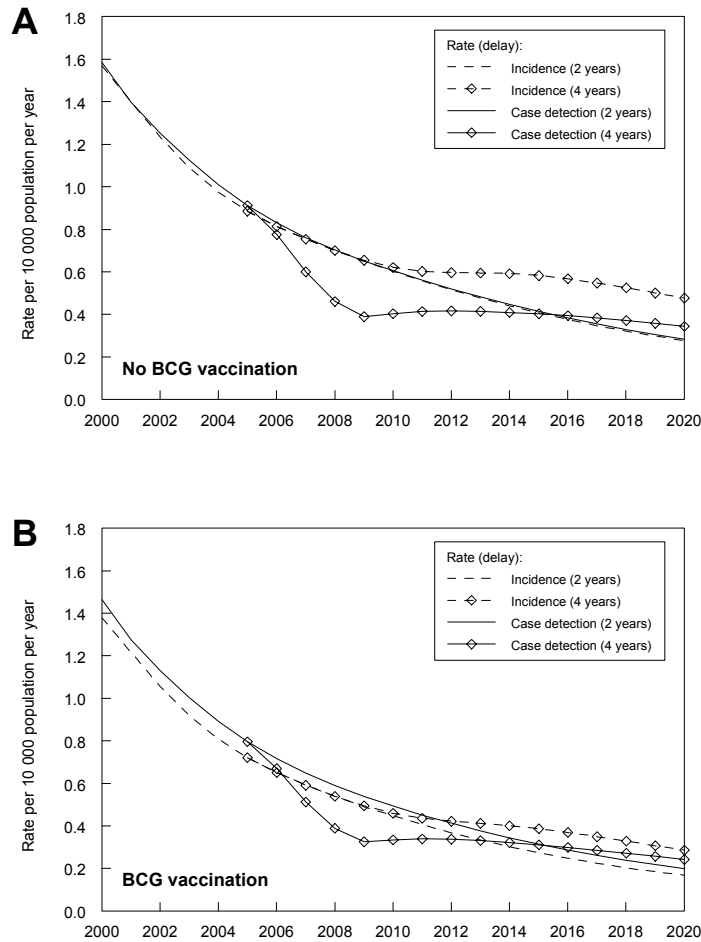
Figure 6.2 Effect of failure to sustain early case detection beyond 2005 on leprosy incidence and case detection. The impact on incidence rate and case detection rate of an increase in the detection delay from 2 to 4 years between 2006 and 2009 is shown for the scenarios from Figures 6.1b and 6.1d. These scenarios assume no transmission during the incubation period and a half-value time for transmission opportunities of 8 years.

decline in incidence rate beyond 2000 is 10.4% (baseline, 10.0%). Doubling the incubation period has the reverse effect of slowing the declines in incidence rate.

Two alternative trends for detection delay up to 1998 were considered: one with decreases in delay that were greater than in the baseline delay trend, and the other with smaller decreases. Of the scenarios with larger decreases in delay, three give a good fit to the reference trend, whereas six of the scenarios with the baseline delay trend had a good fit. This is because with larger decreases, initial delays in detection are longer and

detection backlogs larger, which led to greater increases in simulated CDR during the reference period 1985-1998. When compared to the baseline, the decrease in incidence rate beyond 2000 – when the detection delay has ceased to be longer – is predicted to be somewhat faster (maximum increase, 1.6%). The greatest annual decline was 11.8% (half-value time, 6 years) for the three "good" scenarios, which is the highest decline among all scenarios with a good fit. The maximum annual decline is a little higher (13.5%; half-value time, 5 years), when the five scenarios with a poor fit are also considered. Faster declines were not obtained in this study. The scenarios in which smaller decreases in detection delay were assumed before 1998 had a slower decline in incidence rate beyond 2000 compared to the baseline.

6.6 Discussion

This study addressed two questions: what is the impact of early case detection and MDT treatment on the transmission and incidence of leprosy, and what are the consequences of failing to sustain early case detection?

Early case detection and treatment led to a reduced incidence of leprosy in all scenarios. The time required to halve the incidence rate was 7 years in the most optimistic scenario with BCG vaccination. Slightly faster declines were obtained in the sensitivity analysis. However, much slower declines were found to be possible; half-value times of 14 years with BCG and 43 years without BCG cannot be excluded. A detailed analysis of the predictions indicates that ensuring early detection of contagious patients is the key factor in reducing transmission. Treatment with MDT instead of dapsone monotherapy is also beneficial, because of the lower relapse rates after MDT.

Consequences of not sustaining early case detection

Sustained early case detection is essential for maintaining decreases in transmission and incidence: the predicted decrease slows down when the detection delay increases after 2005. Keeping detection delays short will be more difficult when leprosy incidence decreases, because both the general population and health workers will become less experienced in recognizing symptoms of leprosy.

Leprosy is a public health problem because of the impairments it causes. There may be three million people worldwide with impairments caused by leprosy (*43*). It has been argued that early detection could prevent the development of impairments in more than three-quarters of patients (*44*). Early case detection is therefore also important for prevention of leprosy morbidity.

Trend in detection delay

For most scenarios, the shortening of the detection delay after 1990 resulted in a good fit of the historical trend for the average case detection rate in countries for which data were available throughout 1985-1998. The incidence rate of leprosy in the "good" scenarios

decreased by at most 4.4% per year in this period (Table 6.1: half-value time 15 years). The simulations show that where such declines occur, intensified control may induce a temporary increase in case detection (Figures 6.1b and 6.1d). In recognition of the limited empirical basis for quantifying the detection delay, two additional delay trends were considered in the sensitivity analysis. The impact on incidence predictions was found to be small: detection delays before 2000 did not influence incidence trends far beyond 2000. It could be argued that the 2-year delay used from 1998 onwards is somewhat optimistic (*28, 30, 45, 46*); longer delays would lead to less optimistic predictions about future declines in incidence.

Historical case-detection data

The simulated CDRs increased for more than a decade until 1998, after which control activities were not intensified further. The increase was possible because the simulated CDRs were substantially lower than the incidence rates in 1985 (Figure 6.1). The increase in the historical CDR also lasted more than a decade. Cumulative new cases detected in 1992-1998 exceeded those detected in 1985-1991 by at least 50% in eight of the 14 countries for which historical data on CDRs were available (*1*). This indicates that the differences between case detection and incidence rates must indeed have been substantial.

Information on detection of new cases worldwide is incomplete. Aggregate information is available from 1985 onwards for a group of 33 countries in which leprosy is endemic. Throughout 1994-1998, at least 97% of cases detected globally were detected in these 33 countries (global figures are not available before 1994) (*1*). India detected at least 75% of the cases in this group throughout 1985-1998. The other 13 countries in this study accounted for at least 75% of the remaining cases detected. Thus, the majority of the world leprosy problem was concentrated in the 14 countries that detected at least 2000 cases in 1998 and for which historical CDR data were available throughout 1985-1998.

The figures reported from some countries may be incomplete or contain inaccuracies, and may have been influenced by overdiagnosis and re-registration of previously treated patients (*39*). Nevertheless, the data used in this analysis were the best available. To compensate for limitations in the quality of the data, the CDR increase was allowed to deviate by 50% from the increase in the historical CDR over 1985-1998 while scoring simulated trends as "good". The historical trend in CDR reflects an average pattern of case detection trends, and only in some cases is it representative of the trend in individual countries. However, the robustness of the predicted declines in incidence beyond 2000 has already been indicated. Given the historical trend towards an increase in CDR, autonomous decreases in transmission (e.g. due to socioeconomic improvement) were not considered.

India was counted as one country in the construction of the historical trend. The CDR in India was quite stable over 1985-1998. For each of the three trends in detection delay, we also fitted the scenarios to India alone for the baseline assumptions: this resulted in slower declines in incidence beyond 2000.

Impact of BCG vaccination

The scenario analysis suggests that BCG vaccination is important in reducing the incidence of leprosy, yet for various reasons its impact remains uncertain. BCG vaccination is ignored in half of the scenarios, which is equivalent to making the pessimistic assumption that BCG does not protect against leprosy. The remaining scenarios incorporated optimistic assumptions about the efficacy and coverage of BCG vaccination. Fifty per cent lifelong protective efficacy was assumed. In randomized trials, the protection afforded ranged from 20% to 80%, with low values reported in India (*18, 47*). The assumed trend in coverage is optimistic when compared with data disseminated by WHO (*35*). Thus, the impact of BCG vaccination may have been overestimated in this analysis.

Reasons for variability in predicted incidence trends

The scenarios differ in their assumptions regarding two important unknowns, namely, transmission during the incubation period and waning of transmission opportunities due to rapid transmission to close contacts. These unknowns have led to great uncertainty as to the part played by the policy of isolating patients in the disappearance of leprosy from Norway (*24*). Basic and epidemiological research on transmission is required to improve our understanding of the impact of any strategy for controlling leprosy.

Extrapolation to global case detection

In the year 2000, 720 000 new cases of leprosy were detected worldwide (*1*). In an intermediate scenario with BCG vaccination, it would take about 10 years to halve the incidence rate. If population growth is ignored, extrapolation of this rate of reduction to case detection would imply that 360 000 cases would be detected worldwide in 2010, and 180 000 in 2020. The cumulative number of new patients who will be detected up to 2010 and 2020 is 5 million and 7.5 million, respectively. In the most optimistic prediction, obtained with larger decreases in the detection delay than in the baseline trend (11.8% annual decline in incidence rate), the number of cases detected would be 4 million in 2010 and 5 million in 2020.

Conclusion

The scenario analysis demonstrates that the present leprosy elimination strategy will reduce transmission, although the decline may be slow. Early case detection is the key factor in the success of the strategy. The uncertainties about the rate of decline and the adverse effects of longer detection delays imply that relaxation of leprosy control following the end of the "Final Push" period in 2005, when the target of elimination of leprosy as a public health problem is set to be achieved in all countries, is unjustified. A long-term strategy for leprosy control should be adopted.

6.7 Acknowledgements

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6A Appendix

This appendix details the quantification of the SIMLEP model and provides the values for the parameters used in the sensitivity analysis. A detailed description of the SIMLEP modelling framework has appeared elsewhere (*1*). The information underlying the reference trend for the case detection rate (CDR) that is used in the scenario analysis is also summarized.

6A.1 Model and parameter quantifications

Figure 6A.1 shows the structure of the SIMLEP model. The transitions between compartments are governed by transition rates, i.e. by exponential probability distributions, unless otherwise indicated (see also (*1*)). Tables 6A.1 and 6A.2 list the quantification of the model parameters. Additional information and its sources are given below.

Demographic data

Demographic data for India for 1987, which is close to the middle year of the simulation period, 1960-2020, are used for the birth rate and age-specific death rates (*2*).

Asymptomatic infection

A high percentage (90%) of newly infected individuals are assumed to self-heal without developing any clinical symptoms of leprosy, because leprosy infection is considered to be far more common than leprosy disease (*3, 4*).

The episode of asymptomatic infection represents the time until self-healing for infected individuals who do not develop disease, and the incubation period for those who develop non-contagious self-healing disease or contagious disease which does not self-heal. These forms of disease are referred to in this appendix as PB leprosy (paucibacillary leprosy) and MB leprosy (multibacillary leprosy). The median values of the duration of the incubation periods of PB leprosy (3.5 years) and MB leprosy (10 years) are based on data collected from studies on veterans from non-endemic areas who contracted leprosy after serving in endemic areas (reported minimum and maximum estimates for the median incubation period for veterans with PB leprosy: 2 and 5 years, respectively, and for MB leprosy 8 and 12 years, respectively) (*3*). For those people who did not develop the disease, the length of time until self-healing is equal to the duration of the incubation period for PB leprosy.

Untreated disease and transmission

The incidence of leprosy is based on a ratio of PB to MB disease of 4:1. For PB disease, a self-healing rate of 22.4% per year is assumed in accordance with Sirumban et al. (*5*). The
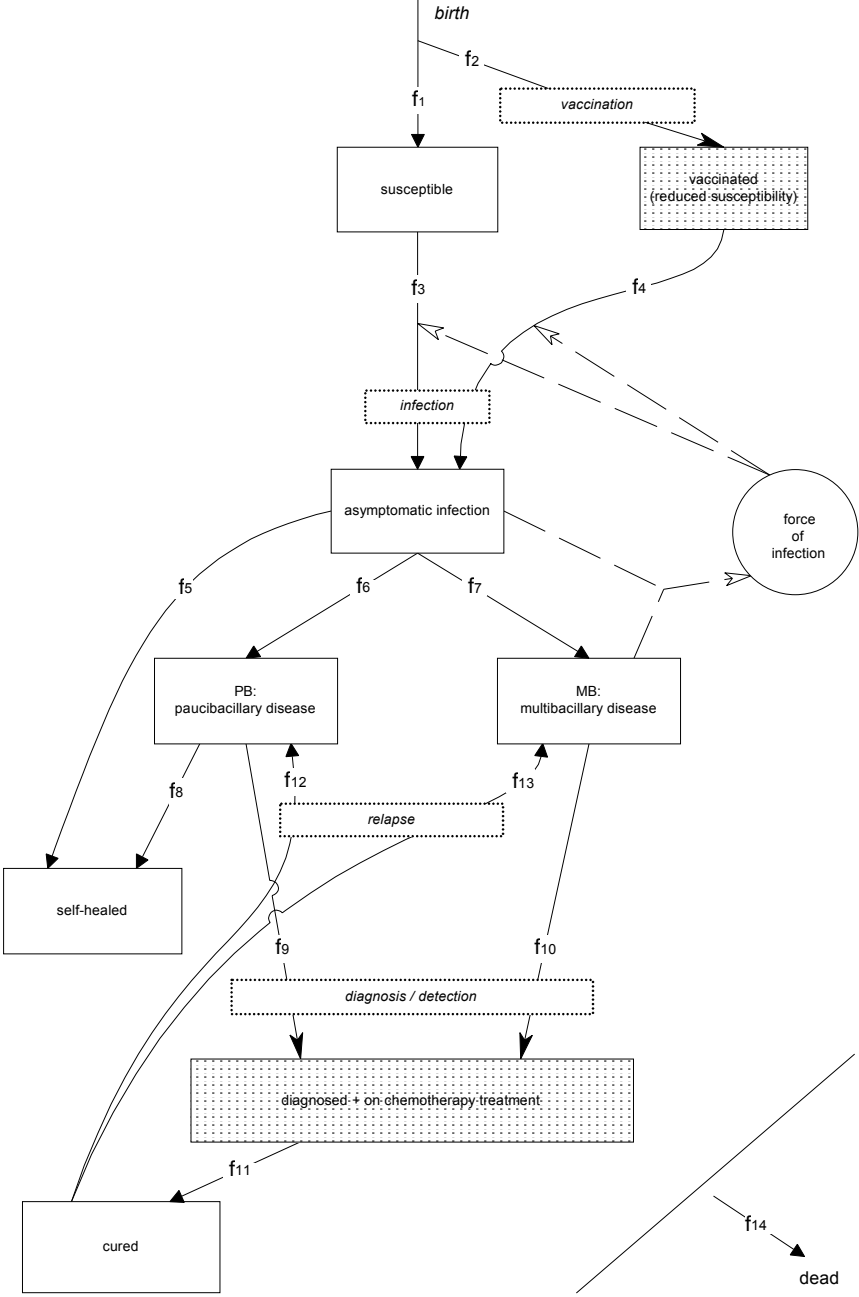
Figure 6.A1 Structure of the SIMLEP model as used in the scenario analysis.

Table 6A.1 Parameter values used in the scenario analysis. [a]

Input parameter	Flows	Value(s)
Demographic data		
Birth rate per 1000 total population per year	f_1, f_2	32.2
Age specific death rates (based on Indian lifetable)	f_{14}	*see text*
Asymptomatic infection		
Percentage among newly infected individuals not developing leprosy disease	f_5	90%
Median duration of asymptomatic infection (Erlang distribution; years)		
– for those not developing leprosy disease	f_5	3.5
– for those developing paucibacillary disease	f_6	3.5
– for those developing multibacillary disease	f_7	10
Disease and transmission		
Percentage of new cases who develop		
– paucibacillary disease	f_6	80%
– multibacillary disease	f_7	20%
Self-healing rate for PB disease per year [b]	f_8	22.4%
Build-up of contagiousness while incubating for MB disease [b]	f_3, f_4	<u>no, yes</u>
Half-value times for waning of transmission opportunities (years)	f_3, f_4	<u>none [c], 2, 4, 8</u>
BCG vaccination at birth: different scenarios		
Application	f_1, f_2	<u>no, yes</u>
Coverage	f_1, f_2	*see text*
Protective efficacy	f_4	50% lifelong
Case detection and chemotherapy treatment		
Mean delay in case detection	f_9, f_{10}	*see text, Table 6A.2*
Mean duration of treatment (years) and drug regimen		
– 1960-1989: dapsone monotherapy	f_{11}	9
– 1990-1999: multidrug treatment	f_{11}	0.8
– 2000-2020: multidrug treatment	f_{11}	0.6
Relapse rate per year		
– after dapsone monotherapy cure	f_{12}, f_{13}	1.5%
– after multidrug therapy cure	f_{12}, f_{13}	0.1%
Proportion of relapsing cases who relapse to (either therapy)		
– paucibacillary disease	f_{12}, f_{13}	10%
– multibacillary disease	f_{12}, f_{13}	90%

[a] Flows refer to Figure 6A.1. Underlined values refer to assumptions that have been varied in the 16 scenarios.
[b] PB = paucibacillary, MB = multibacillary.
[c] Transmission opportunities do not decrease over time.

ratio of PB leprosy to MB leprosy in new case detection depends on the PB to MB ratio for incidence, on the self-healing rate of PB leprosy, and on delays in detection and diagnosis. The reported ratios vary widely between the different regions of the world (see e.g. (*3*)).

Knowledge on the extent of contagiousness and transmission of leprosy is limited. In the scenario analysis, MB leprosy is assumed to be contagious, and in half of the scenarios considered, individuals incubating MB disease are assumed to gradually build up contagiousness. The possibility that patients with PB leprosy and those incubating it are also contagious was not explored. This is because the issue of contagiousness of patients with PB leprosy was considered to be much less important in assessing the possible impact of interventions on transmission than the question of when (which may also be before the onset of disease) transmission takes place.

It is unknown whether the opportunities for an individual to transmit *Mycobacterium leprae* decrease over time. Such a decrease is plausible because close contacts, who are at a high risk of contracting leprosy (*6*), may be infected rapidly. In the scenario analysis, in addition to no decrease, half-value times for transmission opportunities for diseased individuals of 2, 4 and 8 years were considered.

BCG vaccination at birth

In most developing countries, bacille Calmette-Guèrin (BCG) vaccination is given in very young childhood (*7*). BCG vaccination was ignored in half of the scenarios ("no vaccination at all"), which is equivalent to the pessimistic assumption that BCG does not protect against leprosy. In the other half of the scenarios, optimistic assumptions about BCG were made. A policy of vaccination of infants was assumed, starting in 1975 with an initial coverage of 5%, increasing to 80% in 1990, and to 95% in 1999 and all subsequent years. These figures are optimistic when compared to coverages reported by member states to WHO (*8*). Randomized controlled trials have shown that the protective efficacy of BCG against leprosy ranges from 20% to 80% (*9*). The protective efficacy was quite low in Asia, particularly in India where most patients with leprosy are detected (*10-12*), and it is unknown whether the protective efficacy decreases with age. The optimistic assumption of a lifelong 50% efficacy was made.

Case detection and chemotherapy

The delay in detection has a skewed distribution (*13*). Therefore, SIMLEP uses a convolution of two exponential probability distributions for the length of the detection delay (*13*). A trend in mean detection delay was defined using historical information based on recall by patients from areas in which leprosy control is well organized (*13-18*).

The historical trend is summarized in Table 6A.2 (baseline trend in delay). The mean detection delay gradually decreases from an initial 12 years ("no control") to 6 years in 1990, reflecting the gradual establishment of leprosy control programmes. Subsequently, the mean delay decreases to a constant 4 years for 1992-1996, corresponding to the

Table 6A.2 Time trends over 1960-2020 for the mean detection delay.

	Mean detection delay (years)				
	1960-1990	1990-1992	1992-1996	1996-1998	1998-2020
	Decrease	Decrease	Constant	Decrease	Constant
Trend with small decreases in delay	from 8 to 4	from 4 to 3	3	from 3 to 2	2
Baseline trend in delay	from 12 to 6	from 6 to 4	4	from 4 to 2	2
Trend with large decreases in delay	from 16 to 8	from 8 to 5	5	from 5 to 2	2

intensification of control after the 1991 WHA resolution regarding leprosy elimination (*19*). The mean delay then decreases to 2 years in 1998, following the initiation of "leprosy elimination campaigns" (*20*).

In the predictions for the future, two possibilities were considered. The first was that the detection delay remains constant at 2 years until 2020. The second possibility was that the mean detection delay gradually increases from 2 to 4 years between 2006 and 2009, remaining constant thereafter, which reflects possible failure to sustain early case detection and treatment beyond 2005.

The duration of treatment is governed by a single exponential probability distribution for all patients. In the scenario analysis, treatment between 1960 and 1989 was by dapsone monotherapy and, from 1990 onwards, by multidrug therapy (MDT). The choice of a mean duration of dapsone treatment of 9 years was somewhat arbitrary: dapsone was usually prescribed for 5 years for patients with tuberculoid leprosy and for 20 years or for life for patients with lepromatous leprosy (*21*). The prescribed duration of MDT treatment has changed several times, but has always been much shorter than dapsone treatment (*22-24*). The assumed mean duration of MDT treatment (all patients) was less than 1 year (Table 6A.1).

In SIMLEP, the relapse rates after treatment cure are equal for PB and MB leprosy, and are constant over time. A relapse rate after dapsone monotherapy of 1.5% per year was chosen, based on the data of Becx-Bleumink who reported a relapse rate of 0.7% for PB leprosy and 2.5% for MB leprosy (under the assumption that equal numbers of new cases of PB and MB leprosy are detected, the 1.5% rate for all patients and the separate 0.7% and 2.5% rates for PB leprosy and MB leprosy give the same cumulative proportion of relapsed cases after 25 years) (*25*). The reported rates of relapse after dapsone monotherapy vary widely (see e.g. (*25-32*)). Programmes conducted in the field have reported much lower relapse rates after MDT (*6*). A relapse rate for PB and MB patients of 0.1% per year following MDT was used. Using the data of Smith et al. (*33*), 10% of patients with relapses present with PB leprosy, and the remaining 90% with MB leprosy.

6A.2 Sensitivity analysis

Tables 6A.2 and 6A.3 list the different values of the parameters that were used in the sensitivity analysis. Birth rate and age-specific death rates were not varied in the sensitivity analysis. Also, no variation was made in the mean duration of MDT (changes will not affect simulation results), the relapse rate after cure with MDT (this rate is too low to affect simulation results), or in the proportion of those patients who relapse to MB disease (baseline value: 90%; the vast majority of patients who relapse would be expected to have leprosy of the MB type).

Values of parameters that are varied

The values of the baseline parameters are given in Tables 6A.1 and 6A.2. For most of the parameters, the baseline values were halved and doubled for the scenario analysis (Table 6A.3). The exceptions were the percentage of newly detected cases who do not develop leprosy disease (Table 6A.3) and the trend in detection delay (Table 6A.2). The baseline assumption is that 90% of newly infected individuals self-heal without ever displaying any clinical symptom of leprosy. The contrasting assumption is that all newly infected individuals will develop leprosy disease. In the baseline trend in detection delay, the mean delay decreases by 2 years between 1990 and 1992, and by a further 2 years between 1996 and 1998 (Table 6A.2). By contrast, for the trend with small decreases in the delay, the mean delay decreases twice by 1 year and, in the trend with large decreases,

Table 6A.3 Alternative quantifications in the sensitivity analysis. [a]

Parameter changes	Flows	Value(s)
Percentage among newly infected individuals not developing disease	f_5	0%
Median duration of incubation period (years) [b]	f_6, f_7	halved: PB 1.75, MB 5 doubled: PB 7, MB 20
Percentage of new cases who develop MB disease	f_6, f_7	halved: 10% doubled: 40%
Self-healing rate for PB disease per year	f_8	halved: 11.2% doubled: 44.8%
Trend in mean delay in case detection	f_9, f_{10}	small decreases in delay large decreases in delay
Mean duration of dapsone monotherapy (years)	f_{11}	halved: 4.5 doubled: 18
Relapse rate per year after dapsone monotherapy cure	f_{12}, f_{13}	halved: 0.75% doubled: 3.0%

[a] PB = paucibacillary, MB = multibacillary.
[b] Median durations of 1.75 and 7 years were also used for the period of asymptomatic infection for subjects who did not develop disease (flow f_5). The duration of this period had no effect on the scenario predictions.

twice by 3 years. The mean delay of 2 years from 1998 onwards, which corresponds to a median delay of 1.5 years, was used in all three trends for the detection delay.

6A.3 Reference data for case detection rate

The reference CDR during 1985-1995 is calculated as the average of the CDRs of the 14 countries in which at least 2000 cases were detected in 1998, and for which detection figures at country level were reported throughout 1985-1995. The trends in CDR since 1985 are described elsewhere (*34*) on the basis of the reported information (*35-41*). The CDRs per 10 000 total population for the year 1998 and the average annual increases in CDR between 1985 and 1998, derived from the CDRs for these 2 years for the 14 countries are as follows: Bangladesh (1.0; +5.3%), Brazil (2.5; +4.5%), China (0.02; –7.8%), Ethiopia (0.7; –3.6%), Guinea (5.2; +21.8%), India (6.5; +0.3%), Indonesia (0.9; +4.5%), Madagascar (6.1; +9.0%), Mozambique (2.2; +9.2%), Myanmar (3.1; +4.3%), Nepal (3.0; –0.2%), Philippines (0.5; +6.6%), Sudan (0.7; +26.0%) and Viet Nam (0.3; –1.6%). The reference CDR increased from 1.3 per 10 000 total population per year in 1985 to 2.3 in 1998 (average annual increase, 4.6%).

6A.4 References

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7

Factors associated with impairments in new leprosy patients: the AMFES cohort

7.1 Summary

Data on the importance of the delay between onset of symptoms and registration as a risk factor for impairment are sparse. This study investigates the quantitative relationship between this delay, other risk factors and the impairment status in new leprosy patients. It reports on 592 new leprosy patients enrolled in 1988-1992 in the prospective ALERT MDT Field Evaluation Study in central Ethiopia (AMFES). The influence of the risk factors sex, age, delay, PB/MB classification in relation to BI, and prior dapsone treatment on the impairment status at intake is analysed. Estimates for the delay are based on patient recall. For the risk factors, odds ratios on impairment and on severity of impairment were calculated using both univariate and multivariate logistic regression. The registration delay was 2 years or more for 44% of new patients. The prevalence of impairment (WHO impairment grades 1 and 2 combined) increased continuously from 36% for new patients with a delay of 0-1 year to 81% for new patients with delays of 4 years or more. This prevalence also increased continuously with age; it rose from 26% in children to 80% for the age group 60 and over. In the multivariate regression, the odds ratios for new patients to be impaired were statistically significant for all delay categories (baseline 1-2 years) and age groups (baseline 15-29 years). No statistically significant differences in odds ratios were observed with respect to sex and PB/MB classification in relation to BI. Overall, 31% of new patients presented with WHO impairment grade 1 and 23% with grade 2. The risk on grade 2 also increased with the registration delay amongst the impaired new patients. Relatively few impaired males and relatively few impaired MB patients with a BI value of 3 or higher had grade 2 impairment. Registration delay and age are the main risk factors for presentation with impairment. Reduction of delay in central Ethiopia requires re-thinking of control methodologies. The search for ways to reduce delays in diagnosis and treatment should receive high priority in leprosy research and in leprosy control programmes.

7.2 Introduction

The implementation of effective antibacterial treatment for leprosy has shifted the focus in leprosy programmes to prevention of disability. However, many new cases already have impairments and disabilities. Amongst major endemic countries, the proportion of new cases presenting with WHO disability grade 2 was reported in 1995 to range from 6% to 21% (*1*). Several studies showed that the majority of patients who were impaired at release from MDT already had nerve function impairment at the time of registration (*2-4*). This paper documents risk factors for impairment in new cases, which may contribute to the improvement of prevention of disability activities in leprosy control programmes.

Various factors might be associated with the presence of impairment at registration. For example, differences in impairment status at registration have been observed with respect to gender, age at registration, and leprosy type according to clinical classification systems or the WHO paucibacillary / multibacillary (PB/MB) classification (*2-9*). At the same time, higher proportions of MB cases amongst male patients have been documented (*2, 7-10*), and different age distributions for new PB and MB cases have been reported (*9, 11-14*). This implies that interrelations must be taken into account when analysing which factors are associated with the impairment status at registration.

In addition, it is generally believed that a longer delay between onset of disease and registration, here called registration delay, is associated with more impairment. The proportion of new cases with impairments at registration is, for instance, much higher in passively, as compared to actively, detected cases in Malawi (*2*). Richardus *et al* concluded that early diagnosis (and subsequent activities for prevention of disability) could prevent impairments in more than 30% of all patients in a control programme in Bangladesh (*3*), more than any intervention at a later stage could achieve.

Registration delay has been documented in several studies (*7, 8, 10, 15-22*). A study on long term leprosy trends in Thailand showed that important declines in the registration delay coincided with a declining trend in the proportion of cases presenting with grade 2 disability (*17*). A recent study from another area in Thailand revealed a highly significant linear trend in the proportion of new cases with grade 2 disability in relation to the registration delay (*4*). Bekri *et al* concluded that the median registration delay was more than twice as high in disabled as compared with non-disabled patients from Ethiopia (*22*). Wittenhorst *et al* found a highly significant association between registration delay and presence of impairments in new leprosy patients from Zimbabwe (*7*). It is beyond doubt that the presence and severity of impairments are associated with duration of disease (e.g. (*23-27*)). Surprisingly, knowledge on the quantitative relationship between the registration delay and the impairment status at registration in *new* leprosy patients - while simultaneously considering the impact of other, interrelated factors - is very limited.

This paper therefore examines the impairment status at registration as a function of several potential risk factors and their interaction for patients who were enrolled in a

long-term prospective study of the effectiveness of the WHO-recommended MDT regimens under routine leprosy control service conditions. This study, the ALERT MDT Field Evaluation Study (AMFES), is carried out in a selected area within ALERT's leprosy control programme in central Ethiopia. Details of the design of the AMFES study and preliminary results for the new patients who were registered in the first 3 years have been reported upon before (*28, 29*).

7.3 Materials and methods

Case-finding in ALERT's control programme was almost exclusively passive. All new cases from the selected area were eligible for AMFES, but not all patients presenting during the intake period were enrolled, mainly because of limitations in the accessibility of leprosy clinics. The AMFES intake period was April 1988 to March 1993.

Cases who were relapses from previous chemotherapy treatment and newly detected cases with errors in diagnosis or in enrolment procedures were excluded from the present study. The present study involves all remaining newly detected cases who were enrolled in the AMFES study. Patient characteristics included are age, sex, classification, bacteriological index (BI), duration of prior dapsone treatment, impairment status and registration delay. PB and MB patients who received no more than 4 weeks and no more than 16 weeks of dapsone, respectively, were regarded as 'new, untreated', and were included in the study. Impairments are in this paper expressed in terms of the "WHO disability grades" and are, following Reed *et al* (*30*), referred to as "WHO impairment grades".

The type of treatment (PB or MB) was chosen on the basis of clinical classification and skin smears. Skin smears were routinely taken from both earlobes and from at least two skin lesions for all patients, and were repeated after 4 or 8 weeks in case of doubt. For some patients the smear was either not done, or the result was not available for logistic reasons. For clinical classification, the simplified system for field workers recommended by Jopling (which adds BB to the BL group) was used (*31*). Tuberculoid (TT) and borderline-tuberculoid (BT) patients with a negative smear at all sites were normally given PB treatment. Until July 1989, BT patients with BI not exceeding 1 were included in the PB group. Borderline-lepromatous (BL) and lepromatous (LL) patients and those with a positive smear at one or more sites were given MB treatment. For patients with nerve involvement only, lacking skin lesions and whose skin smears were (repeatedly) negative (neural leprosy, NL), assignment of treatment regimen was based on the extent of nerve involvement or on the finding of acid-fast bacilli in a nerve biopsy. In case of any controversy, patients were referred to the AMFES medical officer. In practical terms, many patients correctly classified as PB within this study, would be classified as MB if now used criteria focussing on number of skin lesions or number of body areas affected had been applied (*32*). The assignment of treatment regimen was straightforward for most

patients. More detailed information on procedures for diagnosis, classification and treatment is given by de Rijk *et al* (*29*).

The registration delay is based on patient recall. Health workers first asked what the patient's complaint is, and then tried to find out when any symptoms (e.g. skin lesions, neurological problems, weakness or numbness in hands and feet) were first noticed, relating them to known events if necessary. The health worker recorded the calendar year of the first notice of symptoms, and the registration delay is calculated from the mid-year of this calendar year and the date of registration. For example, a patient who registered on March 5, 1992 and who recalled having first noticed symptoms in 1990 was assigned a registration delay of 1 year and 8 months. In the Results, we will denote this as 1-2 years; this category includes all calculated delays between 1.0 and 2.0 years. If this patient had registered on September 5, 1992, he would have been assigned a delay of 2-3 years. Individuals registering in the same year as or before July 1 of the year following the year in which symptoms were first noticed, are assigned a delay of 0-1 year (i.e. less than 1 year).

The factors associated with increased risk for impairments at the time of registration were analysed both separately and in combination. In the data analysis, odds ratios for risk factors for presentation with impairments at the time of registration were calculated using univariate and multivariate logistic regression. Statistical significance refers to the 5% level. The data analysis was carried out in SPSS.

7.4 Results

A total of 603 new cases were enrolled in the AMFES project. Out of these, four individuals were wrongly diagnosed as having leprosy, and seven had improper enrolment procedures. Thus, 11 new cases had to be excluded from the present data analysis. This paper reports on the resulting 592 newly detected patients.

Profile of AMFES and ALERT patients

The 592 included patients and the new cases detected in the same period by ALERT's routine control programme (*33*) were compared for age, sex, classification and WHO impairment status. Important discrepancies were not observed, and the patients involved in this study are thus considered to be sufficiently representative for new case detection by ALERT in the same period.

Out of the patients involved in this study, 92% reported voluntarily. This confirms the passive nature of case finding by ALERT's control programme in the late 1980s and early 1990s. Table 7.1 shows that the number of males in the study population was almost twice as high as the number of females (male:female ratio: 1.8). The child proportion was 14%, and for approximately half of the patients the age at registration was between 15 and 34 years. The most common clinical classifications were BT and BL. TT and NL cases were rarely seen. Skin smears were taken from all but 14 (13 BT and 1 BL) patients.

Table 7.1 Characteristics of new patients at intake. Percentages are given in proportion to the numbers of patients for which information is available. Numbers of patients for which information is available are given in brackets if information is not available for all newly detected patients.

Total patients				
592				
Gender				
Male	Female			
377 (64%)	215 (36%)			
Age at registration in years				
0-14	15-29	30-44	45-59	60$^+$
83 (14%)	240 (41%)	127 (21%)	97 (16%)	45 (8%)
Ridley-Jopling classification				
TT	BT	BL	LL	NL
6 (1%)	297 (50%)	202 (34%)	84 (14%)	3 (1%)
Bacteriological index (BI) (n=578)				
0	1+2	3+4	5+6	
311 (54%)	53 (9%)	97 (17%)	117 (20%)	
PB / MB classification				
PB	MB			
292 (49%)	300 (51%)			
Subdivision of PB and MB				
PB	MB: BI=0	MB: BI=1+2	MB: BI=3-6	
292 (49%)	37 (6%)	49 (8%)	214 (36%)	
Registration delay in years (n=586)				
0-1	1-2	2-4	4$^+$	
156 (27%)	174 (30%)	168 (29%)	88 (15%)	
Duration of prior dapsone treatment in weeks				
0	1-4	5-16		
499 (84%)	70 (12%)	23 (3.9%)		
WHO impairment grading				
0	1	2		
268 (45%)	185 (31%)	139 (23%)		

None of the TT, and 13 BT patients had positive smears (10 with BI 1 and 3 with BI 2). Forty BL patients had a BI of 1 or 2, and 132 had a BI of 3 or more. The BI was 3 or more for all 84 LL patients but two. Overall, almost half of the patients were smear positive, and more than one third of the patients had high bacterial loads (BI ≥ 3). The group of patients who received MB treatment consisted of 2 NL patients, 12 BT patients
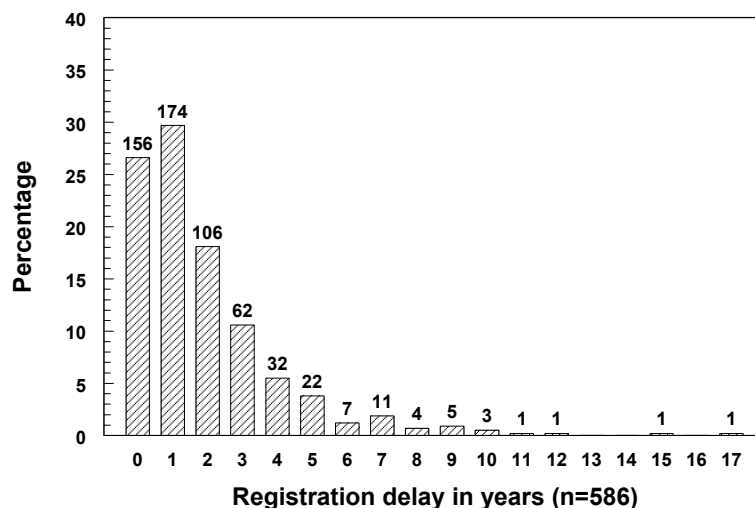
Figure 7.1 Frequency distribution of the registration delay. Numbers of patients for the respective registration delays are given on top of the bars. Years are truncated, e.g. 2 years means between 2.0 and 3.0 years.

(including nine smear-positives with two with BI 2), and all BL and LL patients. Overall, almost equal numbers of patients received PB and MB treatment. For data analysis, patients were re-classified according to a composite classification with four categories (PB; MB: BI=0; MB: BI=1+2; and MB: BI=3+4+5+6). At intake, about 16% of patients had received dapsone treatment (39 PB for at most 4 weeks and 54 MB for at most 16 weeks). The registration delay was above 2 years for 44% of the patients. The mean registration delays for males and females were 2.4 and 2.3 years. Figure 7.1 presents a frequency distribution of the registration delay. Leprosy induced impairments are very common in the study population: 31% of new patients presented with grade 1 impairment and 23% with grade 2.

Univariate analysis of risk factors for presentation with impairment

Table 7.2 gives details on risk factors for presentation with any impairment (either grade 1 or grade 2). The six cases without information on the registration delay were excluded from the analysis. The univariate results indicate that the risk for presentation with impairment strongly increased with both age and registration delay. The proportion with impairment was much smaller for delays below 2 years than for longer delays (42 versus 72%). The overall associations between presence of impairment and age and between presence of impairment and delay were both highly significant (p<0.001). A strong association was also found between risk for any impairment and classification in relation to BI (p=0.002); the risk was highest for MB patients presenting with BI 0, 1 or 2. Males more often presented with impairments than females, but the association was not

Table 7.2 Impairment at intake according to various risk factors with odds ratios for presentation with impairment obtained by univariate and multivariate regression for the 586 new cases with known registration delay.

Risk factor	No. impaired (% of all cases)	Univariate odds ratio (95% confidence interval)	Multivariate odds ratio (95% confidence interval)
Gender			
Male	215 / 372 (58%)	Baseline	Baseline
Female	107 / 214 (50%)	0.7 (0.5-1.0)	0.8 (0.6-1.2)
Classification i.r.t. BI			
PB	150 / 286 (52%)	Baseline	Baseline
MB: BI=0	28 / 37 (76%)	2.8 (1.3-6.2)	2.2 (0.9-5.3)
MB: BI=1+2	35 / 49 (71%)	2.3 (1.2-4.4)	1.6 (0.8-3.2)
MB: BI=3-6	109 / 214 (51%)	0.9 (0.7-1.3)	0.8 (0.5-1.2)
Age (in years)			
0-14	21 / 81 (26%)	0.4 (0.2-0.7)	0.4 (0.2-0.7)
15-29	112 / 238 (47%)	Baseline	Baseline
30-44	85 / 127 (67%)	2.3 (1.5-3.6)	1.9 (1.2-3.0)
45-59	69 / 96 (72%)	2.9 (1.7-4.8)	2.6 (1.5-4.5)
60+	35 / 44 (80%)	4.4 (2.0-9.5)	4.2 (1.8-9.6)
Registration delay (years)			
0-1	56 / 156 (36%)	0.6 (0.4-1.0)	0.6 (0.4-1.0)
1-2	82 / 174 (47%)	Baseline	Baseline
2-4	113 / 168 (67%)	2.3 (1.5-3.6)	2.1 (1.3-3.4)
4+	71 / 88 (81%)	4.7 (2.6-8.6)	4.5 (2.3-8.5)
Prior dapsone treatment (weeks)			
None	264 / 494 (53%)	Baseline	Baseline
1-4	42 / 69 (61%)	1.4 (0.8-2.3)	1.0 (0.6-1.9)
5-16	16 / 23 (70%)	2.0 (0.8-4.9)	2.5 (0.9-6.9)

significant (p=0.07). Short term prior dapsone treatment is associated with a higher but non-significant risk of being impaired at the start of MDT treatment (p=0.17). The higher risk is even not significant when comparing no prior dapsone treatment with prior dapsone treatment up to a maximum of 16 weeks (i.e. prior durations of treatment of 1-4 weeks and of 5-16 weeks are combined, p=0.09).

Multivariate analysis of risk factors for presentation with impairment

Figure 7.2 illustrates the simultaneous impact of registration delay and other risk factors on impairment. With increasing delay the proportion presenting with impairment
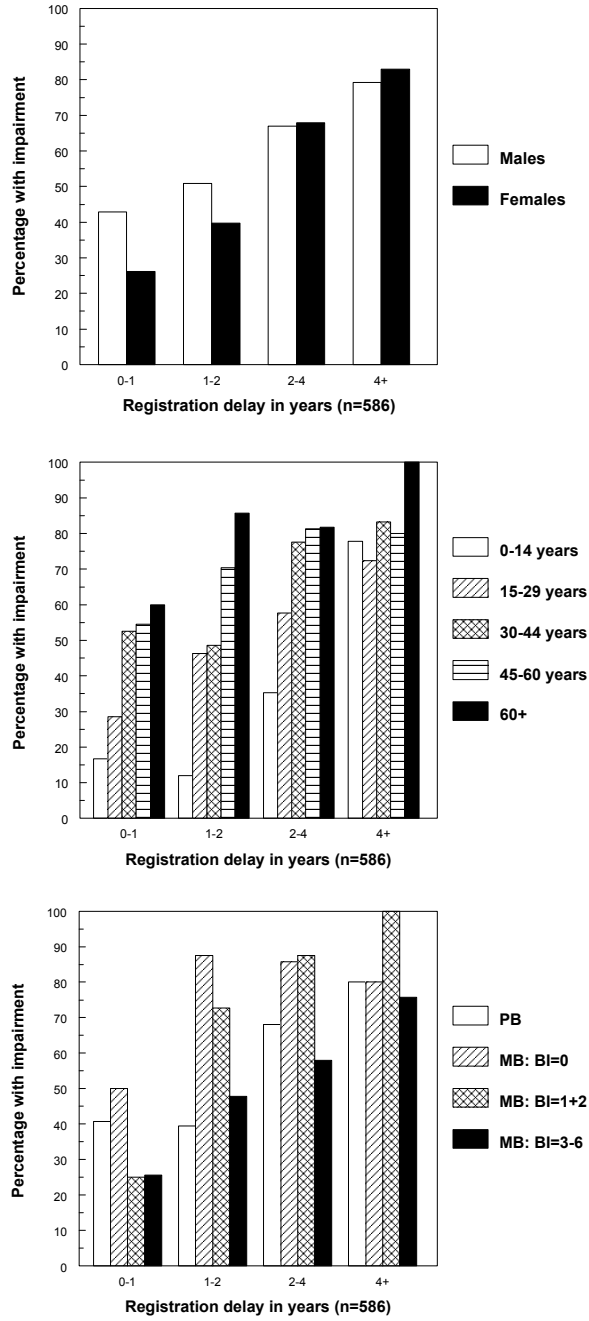
Figure 7.2 Proportions of new patients presenting with impairment according to registration delay in relation to respectively gender, age, and classification in relation to BI.

increases in both males and females, in each age group, and in PB and MB patients irrespective of BI. Only 15% (four out of 27) MB patients with BI 0 and with a delay of 1 year or more presented without impairment. Age influences impairment independently of the registration delay: the proportion with impairment increases with age for all registration delays. An effect of MB in relation to BI on impairment which is independent of the registration delay does not come out clearly.

Table 7.2 gives the results of multivariate logistic regression for a model with all risk factors included. The odds ratios for the significant risk factors in the univariate analysis are pulled towards the no influence value of 1 in the multivariate logistic regression. Details below refer to the multivariate logistic regression. A statistically significant increase in odds ratios is found both for delay and for age. None of the odds ratios for the other risk factors is significant. In particular, the odds ratios for BI 0 and for BI 1+2 have lost their category-wise statistical significance in the multivariate regression; however the differences in risk for the factor classification in relation to BI, with relatively higher risks for MB with BI 0 and MB with BI 1 or 2, are overall significant (p=0.04). The model which includes all risk factors was compared with a multivariate model that was obtained by backward selection of risk factors on the basis of the Wald statistic. Little difference was observed: the odds ratios and confidence intervals for the risk factors included in the model obtained by backward selection (age, registration delay and classification in relation to BI) are very close to those presented in Table 7.2.

Level of impairment

Table 7.3 gives the results of univariate analysis for the risk for impaired new cases to have grade 2 impairment. The multivariate results are not given, because they hardly differed from the univariate results. The risk is higher for long registration delays, but odds ratios for the longer delays are only just significant. The proportion with grade 2 impairment among impaired cases was 31% for delays below, and 52% for delays above 2 years. Figure 7.3 shows that longer registration delays are particularly associated with a higher proportion of grade 2 impairment. The apparent limited influence of longer delays on the proportion with grade 1 impairment must partially be due to an increase in grade 2 resulting from worsening of grade 1, which is largely 'compensated' by individuals who were free from impairment but who develop grade 1 with increasing delay.

Other factors show differences with respect to their influence on the risk of any impairment and on the severity of impairment in impaired cases. Firstly, MB with BI 3 or more gives a significantly lower risk for grade 2 impairment (baseline: PB leprosy). Secondly, there is no increase in the risk of grade 2 impairment with age. In fact, the risk appears to be highest for children and lowest for individuals of age 45 and older. No decrease was found in the mean registration delay with age in impaired new cases. Finally, while overall having less impairments, females with impairment more often had grade 2 than impaired males (53% versus 38%). Figure 7.4 shows that the excess in grade 2 impairment in impaired females as compared with impaired males exists for registration

Table 7.3 Grade 2 versus grade 1 impairment at intake according to various risk factors with odds ratios for presentation with grade 2 impairment obtained by univariate regression for the 322 impaired new cases with known registration delay.

Risk factor	No. with grade 2 impairment (% of all impaired cases)	Univariate odds ratio (95% confidence interval)
Gender		
Male	82 / 215 (38%)	Baseline
Female	57 / 107 (53%)	1.8 (1.2-3.0)
Classification i.r.t. BI		
PB	72 / 150 (48%)	Baseline
MB: BI=0	14 / 28 (50%)	1.1 (0.5-2.4)
MB: BI=1+2	19 / 35 (54%)	1.3 (0.6-2.7)
MB: BI=3-6	34 / 109 (31%)	0.5 (0.3-0.8)
Age (in years)		
0-14	15 / 21 (71%)	3.5 (1.2-9.6)
15-29	47 / 112 (42%)	Baseline
30-44	46 / 85 (54%)	1.6 (0.9-2.9)
45-59	19 / 69 (28%)	0.5 (0.3-1.0)
60+	12 / 35 (34%)	0.7 (0.3-1.6)
Registration delay (years)		
0-1	16 / 56 (29%)	0.8 (0.4-1.7)
1-2	27 / 82 (33%)	Baseline
2-4	58 / 113 (51%)	2.1 (1.2-3.9)
4+	38 / 71 (54%)	2.3 (1.2-4.5)
Prior dapsone treatment (weeks)		
None	116 / 264 (44%)	Baseline
1-4	17 / 42 (40%)	0.9 (0.4-1.7)
5-16	6 / 16 (38%)	0.8 (0.3-2.2)

delays above 1 year and for all age groups. Gender, age, registration delay and classification in relation to BI were all statistically significant risk factors, but prior dapsone treatment was not.

7.5 Discussion

The objective of this study was to examine the impairment status at registration as a function of registration delay, age, classification in relation to BI, gender and prior short term dapsone treatment.
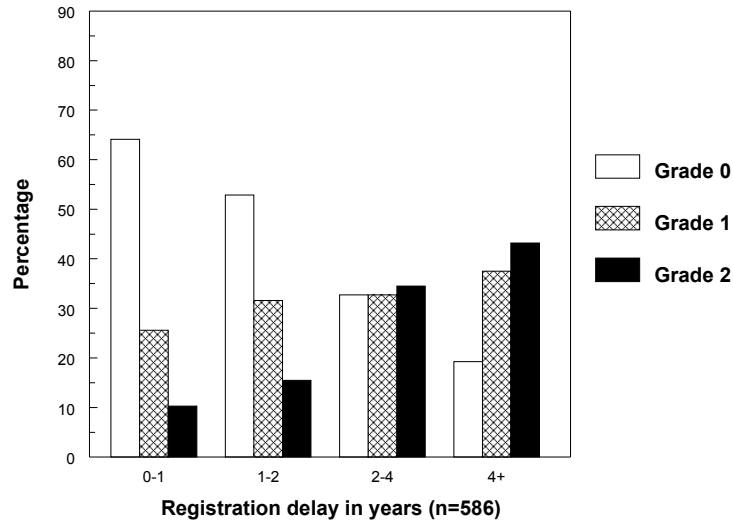
Figure 7.3 Impairment status of new leprosy patients according to registration delay.

Risk factor: delay in registration

This study clearly shows a heavy impact of long registration delay on the impairment status of new leprosy patients from central Ethiopia. Patients with delays below two years had a much smaller chance (42%) of being impaired than patients with longer delays (72%). Among the impaired, similar differences were observed: their chance of grade 2 impairment was 31% for delays below and 52% for delays above 2 years.

The role of registration delay was also addressed in recent studies from Zimbabwe and Thailand. A strong association between delay and grade 2 impairment was shown in the study from Zimbabwe (7). Further analysis of the dataset underlying that study revealed that 41% of patients with a registration delay below 2 years presented with impairment against 60% of patients with longer delays. The proportion with grade 2 impairment among the impaired new patients from Zimbabwe increased from 60% for delays below 2 years to 73% for delays above 2 years.

For Thailand also a significant association with delay was found: 17% of patients with a delay below 2 years had impairments against 23% of patients with longer delays (4). The association between delay and the proportion grade 2 impairment amongst the impaired was particularly strong: 30% for delays below 2 years and 58% for longer delays had grade 2. Biological differences between populations and differences in case detection and assessment methods, methods of interviewing patients and calculation procedures may all underlie differences in results from studies on the importance of the registration delay as a risk factor for impairment. Nevertheless, all the above results are remarkably consistent.
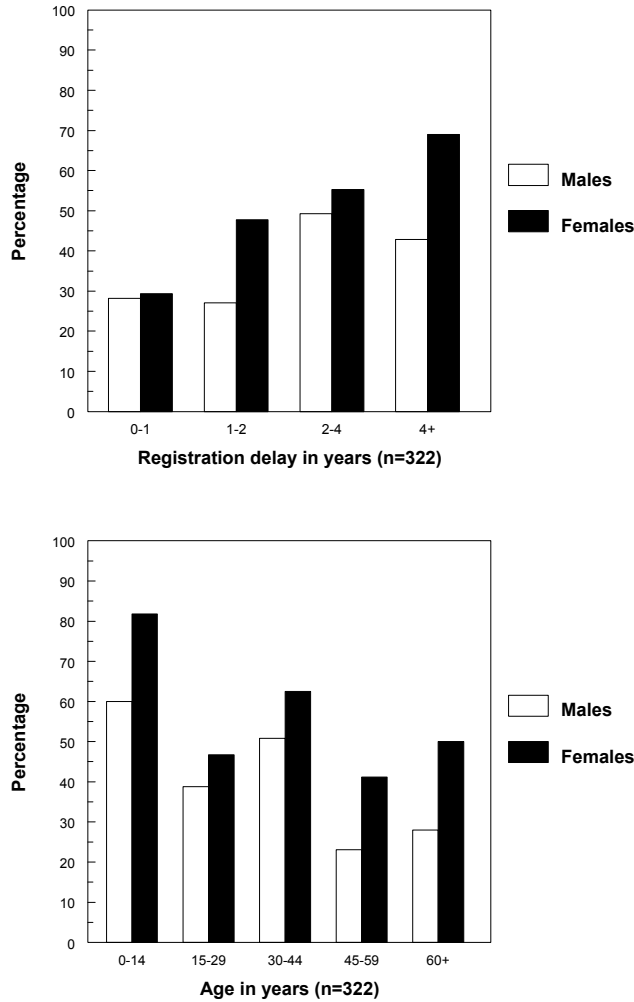
Figure 7.4 Proportion of impaired new leprosy patients presenting with grade 2 impairment according to gender in relation to both registration delay and age.

Risk factor: age

Several studies have reported that the risk of impairment in new cases increases with age (*2, 5, 7, 8*). However, such a univariate association does not occur in the study from Thailand (*4*), and observed univariate associations between age and impairment may be confounded by the registration delay. In the present study, the multivariate analysis shows that the risk of impairment increases with age independently of other risk factors including registration delay. Interestingly, a different effect of age was shown for the risk

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of grade 2 impairment amongst impaired new cases: this study showed this risk to be lowest among the individuals of ages 45 and above. We do not have a straightforward explanation for these age effects. Additional examination of the data presented in the Thailand study (*4*) and of the datasets underlying the Zimbabwe study (*7*) and another recent study from Bangladesh (*9*) did not give further evidence for the finding of a lower risk of grade 2 impairment in impaired new cases of older ages.

Risk factor: classification in relation to BI

MB patients with BI 0, 1 or 2 had the highest risks of impairment. The lower odds ratios in the multivariate analysis are largely explained by the relatively high age of these MB patients. MB patients with high bacterial loads (BI≥3) had relatively few impairments, and had a significantly lower risk of grade 2 once being impaired. Further investigation showed that this risk was significantly lower only for LL patients with BI≥3 in univariate analysis, and for both BL and LL patients with BI≥3 in multivariate analysis. In the present study, all LL patients but two had a BI of 3 or more. Gilbody stated that borderline leprosy is "potentially the most widespread and crippling form of leprosy" (*34*). This is in line with our observation that the risk of grade 2 impairment is lower for LL patients with BI 3 or more, but does not explain our finding that the risk is also lower for the BL patients with BI 3 or more than for the PB patients (all but 7 are BT) and the other MB patients (12 BT, 70 BL, 2 LL and 2 NL). This finding, however, may not be too surprising if one realizes that BL leprosy with BI 3 or more is very close to true LL leprosy in the leprosy spectrum.

Risk factor: gender

Males had impairments more often than females, but this finding was neither significant in the univariate nor in the multivariate analysis. The mean registration delays for males and females were almost identical (2.4 versus 2.3 years). The finding as such that impairments are more common in males than females (although with a non-significant difference) is in line with many reports in literature (e.g. (*2, 4, 5, 8, 9, 18*)). The data underlying the study from Zimbabwe not only show a higher risk in males, but also longer mean registration delays for males as compared to females (3.1 versus 2.1 years).

A significant excess in grade 2 impairment in impaired females was found in the univariate analysis. This excess is difficult to explain (see also Figure 7.4), and its significancy disappeared in the multivariate analysis. Comparison with published data (*4, 8*) and data underlying published reports (*7, 9*) revealed that the proportion with grade 2 impairment among the impaired was higher in males than females from Thailand (*4*) and Zimbabwe (*7*), whereas equal proportions were found for the studies from Chad (*8*) and Bangladesh (*9*).

Other risk factors

In this study, 92 patients received dapsone treatment for a duration of 1-16 weeks before inclusion. In the cohort, significant associations with the risk of impairment were neither found in the univariate nor in the multivariate analyses. It has been reported that dapsone treatment may enhance the risk of nerve function impairment (*35*). Development of new nerve function impairment after the start of MDT has also been observed (*3, 4, 36*). Other risk factors for impairment which have been identified but which were not analysed in the present study include occupation, site of lesions, method of case detection, geographic and socio-economic factors, educational attainment and ethnic group (*6*).

Sources of bias

Registration delays are obtained by asking the patient when he or she first noticed symptoms. In his or her mind, a patient might advance this moment in time, especially in cases of long duration of disease. On the other hand, patients or staff could presume that the duration of disease is of long duration when impairments are present. Clearly, the fallibility of patient's recall of first awareness of symptoms can bias the relationship between delay and risk of impairment, although it is difficult to judge the direction of the effect.

In the present study, the date of registration was combined with the recorded calendar year of first notice of symptoms in estimating the registration delay. We used the mid-year of this calendar year. This inaccuracy will lead to underestimation of the strength of the association between delay and impairment.

Other sources of bias can also not be excluded. Case detection was of a passive nature and differences in awareness of symptoms and in self reporting behaviour can exist. Recall of onset of symptoms may also vary between groups of patients. It may be possible that certain findings from this study (in particular the lower risks of grade 2 impairment amongst the impaired in males and in patients of ages 45 and above) are to some extent related to these sources of bias. On the whole, we still found strong associations between impairments status and risk factors in this cohort. Studies comparing routinely obtained registration delays with delays obtained by carefully designed in depth interviews might give valuable information on the reliability of the registration delay.

Size of the problem

Individuals with grade 1 impairment are at risk of developing more severe impairments and subsequent disabilities. This study has shown that short registration delays are associated with less grade 1 impairment. The size of the impairment problem in new cases is usually only expressed in terms of the proportion with grade 2 impairment. In a report from 1995, this proportion was above 20% in four out of fifteen major endemic countries that together contributed 95% of the world wide new case load with grade 2 impairment (*1*). From this perspective, the 23% grade 2 impairment observed in this study is

disturbingly high. It is encouraging that the proportion with grade 2 impairment reported by ALERT's control services in central Ethiopia was somewhat lower in 1995, 1996 and 1997 than in the early 1990s (*37*). Considering ALERT's presence in the area for a period of over 3 decades, re-thinking of control methodologies is definitely required, although it is also clear that public attitudes towards leprosy cannot be changed easily (*22*).

Implications for research and control

The search for ways to reduce delays in diagnosis and treatment should have high priority in leprosy research and in leprosy control programmes. Research addressing this challenge has recently been conducted in Ethiopia. It was shown that ex-leprosy patients were important advisors for seeking early treatment. Also, 21 out of 31 patients (68%) initially presenting with grade 2 impairment versus 11 out of 48 non-impaired patients (23%) had first sought help from traditional healers instead of directly contacting the general health services (unpublished data from the All Africa Leprosy, Tuberculosis and Rehabilitation Centre (ALERT), Addis Ababa, Ethiopia).

A second study broke down the delay until start of treatment into several components (*22*). It was shown that just over 50% of the delay occurs before the patient seeks any help. Use of some form of traditional medicine accounted for just under one-third of the delay, and delay after attending a recognized clinic accounts for over 10% of the total delay. The delay until the patient's first action and the delay between first action and the first visit to a recognized clinic were significantly longer for impaired patients. High levels of stigma and use of traditional medicine were found to be associated with more impairment when comparing two rural areas of Ethiopia with different impairment rates in new patients.

It is highly questionable whether a shift to active methods of case finding can be cost-effective. In addition, there is already a tendency to integrate leprosy services into the general health services. This calls for proper management of leprosy suspects, and delays in referral for leprosy treatment within the general health services should require special attention. In view of problems with referral, Bekri *et al* suggest that in the Ethiopian context, it would be ideal for diagnosis and the start of treatment to be done at the rural clinic, with examination by a specialist at a later stage (*22*). They also state that reducing stigma is far more complex than imparting knowledge alone, and that health education campaigns must be well planned and sufficiently sophisticated in order to have any impact. A recent review already indicated that gender inequalities should be a point of concern to health services and in health education (*38*). A national advertising programme involving mass media was an integral part of a successful campaign against leprosy in the early 1990s in Sri Lanka (*39*). The potential benefits of well-researched media campaigns need to be investigated.

In conclusion, a better understanding of factors determining delays is of eminent importance for the development of strategies that minimize impairment at registration and thus minimize permanent disability in those who develop leprosy. This has also been

recognized by the Medico-Social Commission of ILEP, which identified investigation of factors influencing delay in diagnosis and treatment for different communities as a major research priority in the context of prevention of disability in leprosy (ILEP: Development of an ILEP co-ordinated programme of research on nerve damage and reactions in leprosy. Internal Report. Draft, June 1998).

7.6 Acknowledgements

7.7 References

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8

Dynamics of impairment during and after treatment: the AMFES cohort

8.1 Summary

This study investigates the dynamics of impairment during and after multidrug therapy treatment for the patient cohort of the prospective ALERT MDT Field Evaluation Study (AMFES). The impairment status was compared at intake, at release from treatment (rft), and at the time of the latest survey between 24 and 48 months after release from treatment (follow-up). The eye-hand-foot impairment score (EHF score), which is the sum of the WHO impairment grades of the eyes, hands, and feet, was used as tool for comparison. In all, 433 out of the 592 patients (224 PB and 209 MB) completed treatment in time and were assessed at release from treatment. The risk of getting impaired was 4% for the 113 PB and 21% for the 91 MB patients who were initially free from impairment. Out of the 111 initially impaired PB patients, 41% recovered or improved and 13% worsened in EHF score. For the 118 initially impaired MB patients, these figures were: recovery or improvement 43% and worsening 13%. Three hundred and twenty-three out of the 433 patients (158 PB and 165 MB) had a follow-up examination in between the next 24 to 48 months after rft. The risks of impairment at follow-up were 6% for the 79 PB and 18% for the 77 MB patients without impairment at rft. Out of the 79 PB patients with impairment at rft, 35% recovered or improved and 28% worsened. For the 88 impaired MB patients, these figures were: recovery or improvement 26% and worsening 27%. Patients showed a tendency to compensate EHF score improvement before rft by worsening after rft and vice versa. The first main conclusion is that the impairment status at intake was by far the most important determinant for future impairment. The second one is that the dynamics of impairment were less favourable after rft than before. Little is known about the long-term fate of leprosy patients with irreversible nerve damage and the associated risk of developing severe secondary impairment. Especially in this era of the leprosy elimination goal, we should give this accumulating patient group due attention in research and health policy agendas.

8.2 Introduction

Newly detected leprosy patients may or may not present with impairments. During and after multidrug therapy (MDT), new impairments may develop, and existing impairments may worsen, remain stable or improve. Many studies have addressed the presence of impairments in newly detected patients (e.g. (*1-7*)). Less attention has been paid to the dynamics of impairment during and especially after MDT treatment. One study addressed patients in Malawi (*8*); other studies were conducted in Asian countries (*3, 5, 9, 10*). The percentage of newly detected patients presenting with impairment varied considerably across these studies. Whereas worsening of impairment status was not negligible, the studies revealed that a majority of patients with impairment at release from MDT already had impairment at registration. In only one of these studies (*5*), the impairment dynamics were evaluated during a follow-up period that extended well beyond release from treatment.

All studies employed WHO disability grades. The use of the term 'disability' is however questionable. According to the International Classification of Impairments, Disabilities and Handicaps (ICIDH) (*11*), disability refers to inability to perform activities due to impairment. Impairment is defined as 'any loss or abnormality of psychological, physiological, or anatomical structure or function'. Under ICIDH, the WHO grades do not reflect disability but impairment (*10*). Following earlier publications (*7, 9, 10*), this paper will therefore use the term 'WHO impairment grade' instead of 'WHO disability grade'. In the generally known 1988 WHO system (*12*), grades are assigned to each eye, hand and foot using a scale with three possible outcomes (0,1,2). The maximum of these six grades, the 'maximum WHO impairment grade', specifies the patient's overall score. The 1988 WHO system has again been updated in 1998 by re-defining the grades for the eyes (*13*).

The maximum WHO impairment grade recognises both first onset of impairment and total recovery of existing impairment. Otherwise, its sensitivity to improvement or worsening of impairments is limited. This is of concern because from patient registration onwards, the performance of the services of a leprosy control programme is expressed in changes in impairment and disability. Accordingly, the 1988 maximum WHO impairment grade has primarily been applied to compare impairment profiles of newly detected patients across countries (*14*). De Rijk *et al* introduced an alternative summary score which uses the sum instead of the maximum of the individual grades for eyes, hands and feet (*15*). Further study of impairment dynamics promoted the so called eye-hand-foot impairment score (EHF score), as demonstrating a higher sensitivity in registering change than the maximum WHO grade (*10*). The EHF score has also been suggested as tool for evaluating the effectiveness of steroid programmes (*16*). The EHF score and the maximum WHO impairment grade share the advantage that their components – the individual grades for eyes, hands and feet – are routinely recorded in leprosy control programmes.

In this paper, the EHF score is applied to investigate the severity and evolution of impairment over time for the cohort of the ALERT MDT Field Evaluation Study (AMFES). Comparisons are made between EHF scores at intake, at release from treatment, and at the latest survey examination between 24 and 48 months after release from treatment. Objectives and interim results of the AMFES study, which is conducted within a routine leprosy control programme in central Ethiopia, were described before by de Rijk *et al* (*15, 17*).

8.3 Materials and methods

Methods of enrolment, diagnosis, administration of fixed-duration MDT and case holding in AMFES have previously been specified (*15*) and reviewed (*18*). The present study involves all enrolled newly detected patients except those who had errors in enrolment procedures or in diagnosis.

Recorded patient characteristics include age, sex, clinical classification and bacteriological index (BI). The type of treatment (PB or MB) was chosen on the basis of clinical classification and skin smears. For clinical classification, the simplified system for field workers recommended by Jopling (*19*) was used. It should be recognized that many patients correctly diagnosed as PB in the present study would be classified as MB if presently used criteria focussing on number of skin lesions or number of body areas affected had been applied (*13*).

AMFES patients were scheduled for examination at intake, while on MDT, at release from treatment, at 3 and 6 months after release from treatment (rft) and thereafter at intervals of 6 months. Examination involved the recording of the WHO impairment grades for the eyes, hands and feet according to the 1988 WHO grade definitions (*12*). The maximum WHO impairment grade and the sum of these six impairment grades for the eyes, hands and feet – EHF score (ranging from 0 to 12) – follow directly. This paper investigates the dynamics of impairment by comparing the EHF scores at three different points in time: intake, release from treatment, and the time of the latest survey conducted between 24 and 48 months after release from treatment. A considerable number of patients did not complete treatment, and some patients did complete treatment in due time but were not examined at release from treatment. Patients who did complete treatment and who were examined at release from treatment are referred to as 'rft-patients'. Those among the 'rft-patients' who in addition had a survey examination between 24 and 48 months after release from treatment are in this study denoted as 'follow-up' patients. Unless indicated otherwise, the term 'worsening' will refer to any increase in EHF score (this includes onset of impairment in previously unimpaired patients). 'Improvement' refers to a decrease in EHF score, while 'recovery' indicates that the EHF score has decreased to zero from a previously positive score.

In the data analysis, statistical significance refers to the 5% level. Frequency distributions were compared using the Chi-square test. The data analysis was carried out in SPSS.

8.4 Results

A total of 603 new patients were enrolled in the AMFES project. Out of these, 11 patients were excluded from the present data analysis because of either incorrect enrolment procedures or incorrect diagnosis. The resulting study cohort consists of 292 PB and 300 MB patients.

The cohort over time

Out of the 592 patients, 454 patients completed treatment in time. The treatment completion rates were higher for PB than for MB patients (PB: 242/292, or 83%, against MB: 212/300, or 71%, p<0.001). Thirteen patients died before they could be released from treatment, 104 did not complete treatment and were lost to follow-up, and 21 did not complete treatment in due time but were seen later. Twenty-one patients completed treatment in time but were not examined by the leprosy control supervisor (LCS) at the end of treatment. So, 433 (224 PB and 209 MB) patients completed treatment in time and were examined by the LCS at release from treatment.

The 433 rft patients differed from the other 159 patients in the cohort in several respects. Summarizing, the rft group included more children (PB: 22% against 7%, p<0.01; MB: 11% against 5%, p=0.1). As compared to the non-rft group, the MB rft patients more often had high BI values (BI ≥ 3; 75% against 63%, p<0.05) and less often had EHF scores of 3 or more (28% against 41%, p<0.05). The percentage with EHF score 3 or more was 25% for both PB rft and non-rft patients.

Out of the 433 rft patients, 323 patients had a follow-up examination between 24 and 48 months after rft (158/224 PB, or 71%, against 165/209 MB, or 79%; p<0.05). In comparing these 'follow-up' patients with the 110 rft patients without follow-up (66 PB and 44 MB), again differences are observed. Females were under-represented in the follow-up group of PB rft patients (37% against 52%, p=0.05). The age distributions of the PB rft patients with and without follow-up also differed significantly. In the follow-up group, children were over-represented (25% against 15%) and young adults (ages 15-29 years) were under-represented (30% against 52%). In MB patients, the percentages of females were similar (31% against 30%), whereas children and young adults together were over-represented in the follow-up group (58% against 41%, p=0.05). The rft patients with follow-up did not differ significantly from the rft patients without follow-up in percentage with BI 3 or more (MB patients only), percentage with EHF-score 3 or more (PB: 27% against 20%, MB: 28% against 25%) and percentages improving (including recovery) and worsening in EHF score between intake and rft.

Impairment at intake

Table 8.1 gives details of impairments at intake. About half of the patients had no impairment. Five percent of both PB and MB patients had just one extremity or eye affected with WHO grade 1 (EHF score 1). Thirty-three of PB and 39% of MB patients had EHF scores ranging from 2 to 4. The percentages with EHF score 5 or more were

Table 8.1 Comparison between maximum WHO impairment grade and eye-hand-foot (EHF) score at intake for patients who completed treatment and who were assessed for impairment grades of eyes, hands and feet at release from treatment ('rft patients').

Maximum WHO grade	EHF score								Total	Percentage (%)
	0	1	2	3	4	5	6	7+		
PB patients										
0	113								113	50%
1		11	29	6	6				52	23%
2			16	11	7	4	11	10	59	26%
Total	113	11	45	17	13	4	11	10	224	
Percentage (%)	50%	5%	20%	8%	6%	2%	5%	4%		100%
MB patients										
0	91								91	44%
1		10	45	11	9				75	36%
2			5	5	7	10	11	5	43	21%
Total	91	10	50	16	16	10	11	5	209	
Percentage (%)	44%	5%	24%	8%	8%	5%	5%	2%		100%

11% for PB and 12% for MB. Between PB and MB, no significant differences were observed in percentage with any impairment (PB: 50%, MB: 56%) and with WHO grade 2 impairment (PB: 26%, MB: 21%). PB patients with EHF scores ranging from 2 to 4 more often had at least one extremity or eye affected with WHO grade 2 than MB patients (PB: 45%, MB: 21%, p=0.001). All patients with EHF score 5 or more had at least one extremity or eye with grade 2 impairment. Further analysis showed that, with two exceptions for both PB and MB, they all had at least four extremities affected (for this analysis both eyes are included with the hands and feet to give a total of six 'extremities'). The large majority of the group of all impaired patients had at least two extremities affected (PB: 76%, MB: 87%). 5/224 (2%) PB patients and 3/209 (1.4%) MB patients had eye impairment: all these patients, except one PB patient, had only grade 1 eye impairment. After re-examining patients with eye problems, data on eyes were corrected to refer to eye impairment that is due to leprosy only. Eye impairment figures earlier presented by de Rijk *et al* were therefore higher (*15*). Overall, the distribution of EHF-scores did not differ significantly between PB and MB patients.

Dynamics of impairment in PB patients

Figure 8.1 summarizes changes in impairment over time for the PB patients. Four of 113 (4%) patients free from impairment at intake had impairment at rft. At the same time,
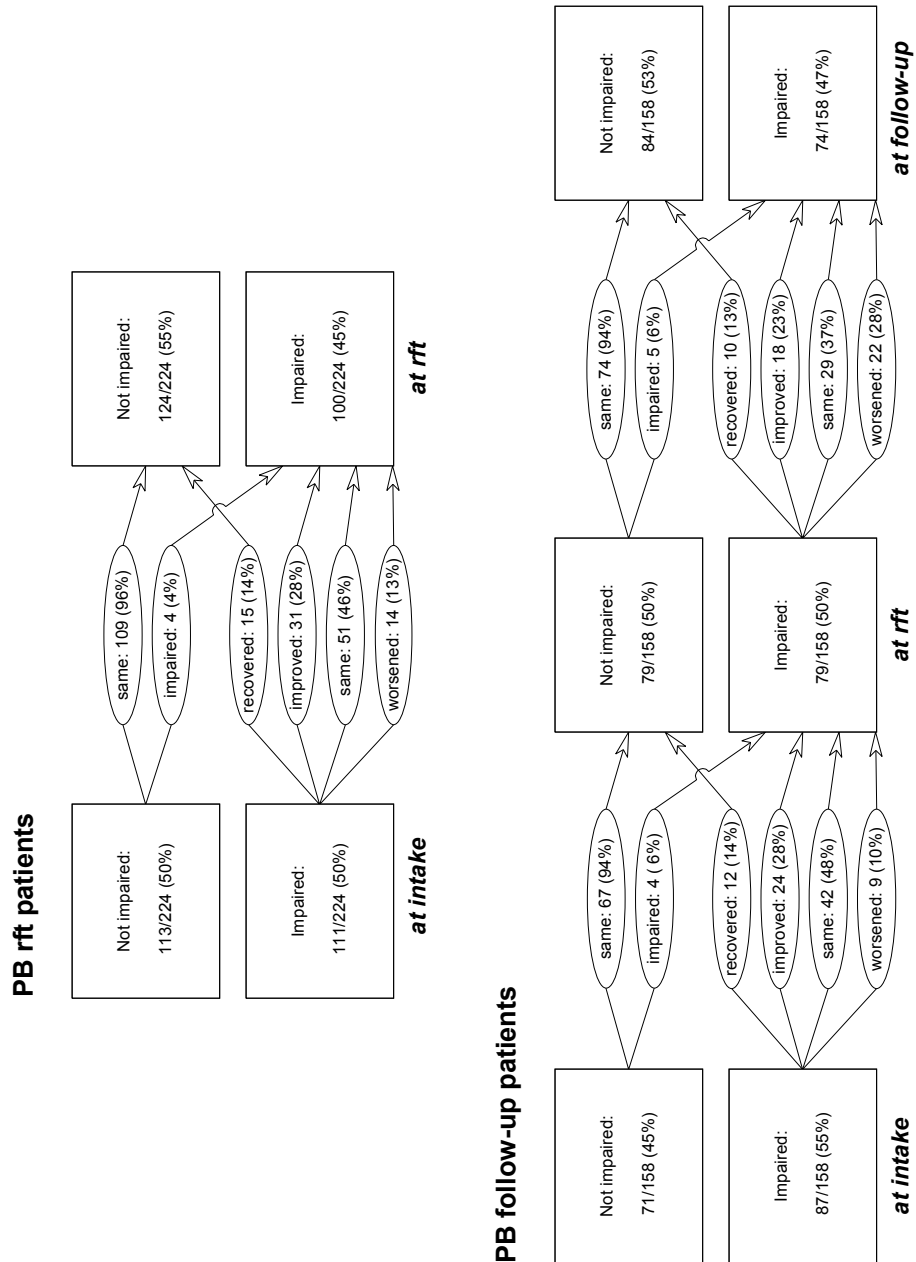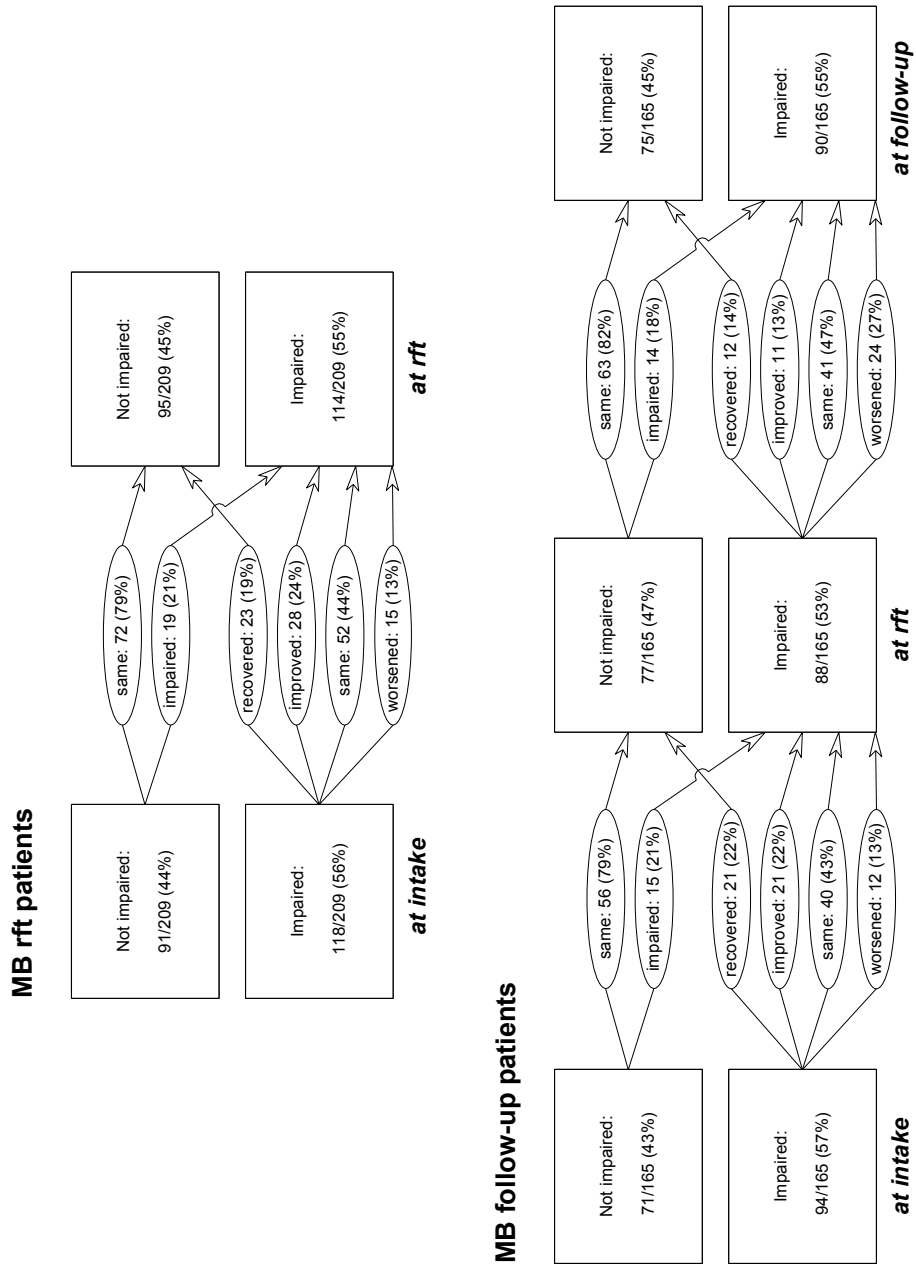
Figure 8.1 Changes over time in impairment status as measured by the eye-hand-foot (EHF) score for PB patients who completed treatment and whose impairment grades were assessed at release from treatment ('PB rft patients'), and for PB rft patients who in addition were assessed for impairment grades between 24 and 48 months after release from treatment ('PB follow-up patients').

15/111 (14%) initially impaired patients recovered from their impairment. These changes imply that the vast majority of patients with impairment at rft (96 out of 100) already had impairment at intake. Overall, improvement including recovery was more common than worsening (which includes onset of impairment, 46 versus 18 patients). Nearly half of the initially impaired patients (46%) did not change in EHF score.

Between rft and follow-up, the numbers of patients improving or recovering and worsening were very similar with 28 and 27. Having impairment at rft is by far the most important determinant for having impairment at follow-up: 69/74 (93%) of those with impairment at follow-up were already impaired at rft.

Table 8.2 shows the relation between changes in EHF score in the two consecutive time intervals. A tendency for compensating changes is most noteworthy. Out of those who improved or recovered during treatment, 33% (12/36) worsened in EHF score after rft, compared to 12% (15/122) for those who stayed the same or worsened during treatment (p<0.005). Similarly, 62% (8/13) of patients who worsened during treatment improved or recovered after rft, versus only 14% (20/145) of the others (p<0.001).

EHF score change does not necessarily reflect a patient's impairment dynamics well because improvement in one extremity or eye may coincide with worsening in another. Between intake and rft, this actually happened in three patients (the EHF score did not change in one and improved in two of them). Further analysis revealed the same

Table 8.2 Relation between changes in eye-hand-foot (EHF) score between intake and treatment completion ('intake → rft') and between treatment completion and latest assessment between 24 and 48 months after treatment completion ('rft → follow-up') for patients who completed treatment and were assessed for impairment grades at release from treatment and in the post-treatment period (percentages of all patients in brackets). In the table, 'improvement' refers to any gain and 'worsening' to any loss in EHF score.

Change in EHF score (intake → rft)	Change in EHF score (rft → follow-up)			
	Improvement	No change	Worsening	Total
PB patients				
Improvement	8 (5%)	16 (10%)	12 (8%)	36 (23%)
No change	12 (8%)	84 (53%)	13 (8%)	109 (69%)
Worsening	8 (5%)	3 (2%)	2 (1%)	13 (8%)
Total	28 (18%)	103 (65%)	27 (17%)	158 (100%)
MB patients				
Improvement	2 (1%)	20 (12%)	20 (12%)	42 (25%)
No change	10 (6%)	72 (44%)	14 (8%)	96 (58%)
Worsening	11 (7%)	12 (7%)	4 (2%)	27 (16%)
Total	23 (14%)	104 (63%)	38 (23%)	165 (100%)

phenomenon in seven patients after rft. One of them worsened, two did not change and four improved in EHF score. These opposite changes imply that 35% (28/79) of the already impaired follow-up patients worsened in at least one eye or extremity during follow-up, against 28% (22/79) who worsened in EHF score.

Further analysis revealed the maximum change in EHF score between intake and rft to be three points: one rft patient worsened, and two rft patients improved by three points. The change was at least two points in 33% of all worsening patients, and in 16/39 (41%) of improving patients with an initial EHF score of 2 or more (including eight recoveries). Between rft and follow-up, two patients worsened, and four patients improved by three points or more. The change between rft and follow-up was at least two points in 41% of all worsening patients, and in 15/25 (60%) of improving patients with an EHF score of 2 or more at rft (including seven recoveries). Overall, no important changes occurred over time in the distribution of EHF scores for PB patients as a group; the differences between intake, rft and follow-up were not statistically significant for the rft patients, nor for the follow-up group (EHF score categorization used: 0, 1, 2, 3-4, 5-6, 7-12).

Dynamics of impairment in MB patients

The EHF score changes for the MB patients are summarized in Figure 8.2. In the MB group, recovery of existing impairment (23 patients) between intake and rft is largely compensated by first onset of impairment (19 patients). Still, the vast majority of patients with impairment at rft were also already impaired at intake (95/114, or 83%, against 96% for PB). Improvement plus recovery again occurred more often than worsening (51 versus 34 patients). Over 40% of initially impaired patients (44%) did not change in EHF score.

Between rft and follow-up, less patients improved than worsened in EHF score (23 versus 38 patients). In comparison to earlier change, impaired patients less often improved or recovered (23/88, or 26% against 51/118, or 43%, before rft) and about twice as often worsened (24/88, or 27%, against 15/118, or 13%). Again, presence of impairment at rft is by far the most important determinant for later impairment: 76/90 (84%, against 93% for PB) patients with impairment at follow-up also had impairment at rft.

A tendency for compensating changes similar to that for PB patients is observed (Table 8.2). Out of those who improved or recovered during treatment, 48% (20/42) worsened in EHF score after rft, compared to 15% (18/123) for those who stayed the same or worsened during treatment (p<0.001). Also, 41% (11/27) of patients who worsened during treatment improved or recovered after rft, versus only 9% (12/138) of the others (p<0.001).

WHO impairment grades of extremities and eyes also simultaneously changed in opposite directions in MB patients. Out of the nine patients who experienced this before rft, three improved in EHF score and six maintained their score. Because 13% (15/118) of the

Figure 8.2 Changes over time in impairment status as measured by the eye-hand-foot (EHF) score for MB patients who completed treatment and whose impairment grades were assessed at release from treatment ('MB rft patients'), and for MB rft patients who in addition were assessed for impairment grades between 24 and 48 months after release from treatment ('MB follow-up patients').

patients with impairment at intake worsened in EHF score, this implies that 20% (24/118) of them worsened in at least one eye, hand or foot. After rft, only two MB patients experienced simultaneous improvement and worsening (one worsened and two of them did not change in EHF score).

Further analysis also demonstrated notable changes in the MB patients. Between intake and rft, six rft patients worsened, and eight rft patients improved by three EHF points or more. The total change was at least two points in 47% of all worsening patients, and in 33/47 (70%) of improving patients with an initial EHF score of 2 or more (including 19 recoveries). Between rft and follow-up, six patients worsened, and one patient improved by 3 points or more. The total change between rft and follow-up was at least two points in 34% of all worsening patients, and in 10/20 (50%) of improving patients with an EHF score of 2 or more at rft (including nine recoveries). Statistically significant differences in the EHF score distributions over time were not observed for the MB patients.

8.5 Discussion

The present study confirms the earlier indication that the AMFES cohort is severely affected by impairment and disability (7). Many patients were impaired at intake, frequently with WHO grade 2 and usually with multiple extremities involved. More than 10% of both PB and MB patients had EHF scores of 5 or more. Such scores imply very extensive nerve involvement.

Dynamics of impairment over time

The dynamics of impairment over time were illustrated by comparing EHF scores between intake and rft, and between rft and follow-up survey. Only a minority of patients with impairment at intake recovered completely. Impairment at the previous assessment was the most important determinant for impairment at the next. The dynamics of impairment were less favourable after rft than before. The risk of becoming impaired was both before and after rft significantly lower for PB than MB patients without previous impairment. During both periods, more than half of the impaired PB and MB patients changed in EHF score. A tendency towards compensation of EHF score improvement before rft by worsening after rft and vice versa was observed. Overall, the EHF score distributions of the PB and MB groups hardly changed over time.

Although the differences in the EHF score distributions at the different assessments were not statistically significant, the dynamics of impairment after rft deserve special attention. Compared with the treatment period, both PB and MB patients with impairment showed further worsening of their EHF score after rft twice as often. The EHF score measures both primary and secondary impairments. The development of primary impairments (sensory loss and muscle weakness) relates to active neuritis which, although it occurs, is much less common after rft than before (20). The worsening of the EHF score after rft is therefore likely to be due to increasing secondary impairment (wounds, ulcers and tissue

loss), although the AMFES database does not contain this information in detail. This is in accordance with the suggestion from a study from Thailand that with longer periods after rft, changes in impairment status will more and more be due to new/increased tissue damage (e.g. wounds, bone loss) than to increases in NFI (*5*).

Drop-out rates in our study were considerable. The greatest number of losses occurred at the time of the overthrowing of the former Ethiopian government in 1991 (*18*). Probably, the longer duration of MB treatment contributes to the lower treatment completion rates in MB as compared to PB patients (71% versus 83%). In contrast, follow-up of rft patients was more successful in the MB group (79% examination versus 71% for PB). The drops-outs before and after rft differed from the other patients in several respects. Significant differences in EHF score change before rft were not observed between patients who did and did not drop-out after rft. It must be noted that patients who experience complications may at times both be more prone (need for extra care) and less prone (due to loss of confidence in the programme, or hiding because of stigma) to complete treatment and to present at follow-up examinations.

Studies that address change in impairment over time (*3, 5, 8-10*) are difficult to compare because of differences in case definitions, treatment durations and scoring systems for impairment. Still, all these studies found that clear majorities of patients with impairment at rft already had impairment at registration. One study also addressed change after rft (*5*). In contrast to our study, the risks of worsening after rft were lower (but still significant) than before for MB patients and similar for PB patients. The EHF score was only utilized in two studies from Nepal (*9, 10*). Both studies addressed the same group of MB patients at diagnosis and examination after two years of MDT. The percentage with impairment at diagnosis (44%) was identical to our MB group. Although the percentage of patients with EHF scores of seven or more was higher in the Nepal group (6% versus 2%), the EHF score distributions at diagnosis were overall rather similar. Differences in the EHF score dynamics between the Nepal study and our study (usually rft was also two years later than intake) were observed, but a consistent pattern was not observed.

The dynamics of the EHF score after rft are worrisome. In addition, little is known about the long-term fate of leprosy patients who have irreversible nerve damage. The years of life lost to disability in this patient group, which accumulates over periods of many years, represents the real burden of leprosy disease. More insight into the size of this group, in the health related problems that they experience, in the care and support that they judge appropriate and in the associated resource requirements is urgently required. This patient group should get the attention in health policy agendas that it is entitled to.

Reflection on the use of the EHF score

We chose the EHF score as the evaluation tool for the present study. The EHF score gives a more detailed picture of the impairment status than the maximum WHO grade. In one of the two papers from Nepal, van Brakel *et al* showed the EHF score to be much more sensitive than the maximum WHO impairment grade: 37% of patients who

changed in EHF score did not change in maximum WHO grade (*10*). Further analysis showed this difference to be more pronounced in our study.

We agree with van Brakel that the EHF score is not a perfect impairment indicator: it remains a simple sum of the WHO impairment grades of the extremities and eyes. A point of criticism with respect to summary scores such as the EHF score is that they are unable to discriminate between a major change in one component and minor changes in several components. But for the WHO grades for extremities and eyes that make up the EHF score, van Brakel *et al* stated that "a change of one point at any site usually constitutes a major change in impairment status" (*10*). In extremities that improved in WHO impairment grade upon corticosteroid treatment, Broekhuis *et al* showed the changes in sensory testing (ST) and voluntary muscle testing (VMT) to be important (*16*). Nevertheless, the EHF score may mask simultaneous changes of extremities and eyes in opposite directions. The frequency with which this happened in our study group is however not alarming.

The reliability of the EHF score has not yet been established. To our knowledge, the retrospective study by Broekhuis *et al* (*16*) is the only study that investigated the reliability question. They indicated the Hand-Foot impairment score (sum of the WHO grades for extremities: HF score) to be a promising device for the evaluation of the effectiveness of corticosteroid treatment at programme level. They also demonstrated that the EHF score is not a suitable device for supporting individual patient management.

Unfortunately, it is not possible to validate the EHF score on the basis of the AMFES cohort. The main reasons for this are lack of detailed information on secondary impairment and the fact that the monitoring of AMFES patients was less close after rft. Compared with other scoring systems, the EHF score has some important advantages. It is simple, reproducible, and information on its components (the WHO impairment grades for extremities) is already routinely collected in many control programmes (*16*). Although we acknowledged a number of deficiencies in the EHF score, we are convinced that they are outweighed by the practical usefulness of the EHF score. Following van Brakel (*10*) and Broekhuis (*16*), we therefore strongly recommend initiation of prospective validation studies of the EHF score as tool for the evaluation of activities at programme level.

8.6 Acknowledgements

8.7 References

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9

Discussion

In this chapter, the research questions formulated in Chapter 1 are answered (9.1). Next, the prospects for reducing the global prevalence of impairment caused by leprosy are evaluated on the basis of the findings presented in this thesis (9.2). Finally, general conclusions and recommendations are given (9.3).

9.1 Answering the research questions

Question 1

What were the trends in leprosy case detection rates in recent decades?

Answer

The observed trends in leprosy case detection rate (CDR) vary widely between different areas and countries. Persistent declines, stable trends and trends with strong fluctuations are all observed. One major endemic country, Brazil, differs from all others: its CDR increased during almost three decades. In the 1990s, the CDR was stable or increased in many countries.

Comment

Chapter 2 presents a literature review of trends in leprosy case detection rates (CDRs) that were published in international literature. The 16 selected trends all covered at least ten years, including 1982-1987. For 13/16 areas and countries, the trends were declining by at least 2% per year. A rather stable trend was observed in one area, a district in India, and the Brazilian CDR increased from 1970 until the end of the observation period in 1987. In one country, the CDR did not show a clear pattern. It was already noted in Chapter 2 that the literature review may have suffered from publication bias: a tendency to publish on high-quality control programs covering long periods of time or indicating successful leprosy control cannot be excluded.

By combining information from different sources, CDRs were also derived from 1985 to at least 1998 for 14 countries with high case loads, see Chapter 3. These 14 countries accounted for the vast majority of the global case detection during 1985-1998, also when India is excluded (in 1998, India accounted for almost 80% of global case detection). The CDRs of these 14 countries showed a less favourable picture than the literature review. For only four countries, a decreasing tendency was observed, either during 1985-1998 as a whole or in more recent years. The CDRs were rather stable or increased for the other ten countries, which included India and Brazil. For some of these countries, sudden sharp increases in CDR were observed in the late 1990s. The increase in CDR in Brazil that started in 1970 persisted until the late 1990s. In terms of annual number of cases detected, Brazil always ranked second after India during 1985-1998. Although available information is not entirely complete, the data from Chapter 3 suggest that the global CDR may have decreased slightly at best.

Question 2

Can the observed trends in leprosy case detection in recent decades be explained, and do the available data provide evidence for an impact of leprosy control on transmission?

Answer

Available data do not suffice for disentangling possible causes for observed downward trends in case detection. BCG vaccination may have been important in some areas, but not in others. There is no evidence for an impact of early case detection and chemotherapy on transmission. Most likely, the observed increases in case detection in the 1990s are the consequence of intensification of case detection efforts.

Comment

Both reduced transmission and reduced detection efforts may lead to reductions in case detection. The literature review from Chapter 2 suggests that several factors may have reduced transmission in different areas/countries, but hard evidence is not provided. Findings are summarised below. Case detection trends in the 1990s have undoubtedly been influenced by intensification of leprosy control (Chapter 3).

Socio-economic improvement

The papers reviewed hardly provide information on socio-economic improvement, although it is suggested that geographical differences in economic growth may have led to differences in declines in CDR within China. Further information shows that there was often at least some socio-economic improvement, which may have contributed to declines in CDR. Two crude indicators for improvement, female illiteracy rate and life expectancy at birth, improved in both the 1970s and 1980s in almost all countries of the literature review (CDR trends up to 1993 were reviewed) (*1*). A third indicator, the gross domestic product (GDP) per capita, increased for most countries in the 1970s but this growth often did not persist.

BCG vaccination

BCG was incorporated in the Expanded Programme on Immunization (EPI) of infants in 1974. Infant vaccination can only have a substantial impact on CDRs after many years because children constitute a minority in leprosy case detection. The reviewed papers do not suggest a general impact of BCG on trends, because there were no indications of high BCG coverages before 1974, or of vaccination not being confined to infants, with one or two exceptions. BCG probably did influence the decline in CDR in Malawi, because it was introduced in 1972 in mass campaigns aiming at individuals under 15 years of age (*2*) and because the protective efficacy of BCG in Malawi was at least 50% (*3*). The potential impact of infant BCG vaccination may be limited because the protective efficacy of BCG varies widely between populations, and because the efficacy may wane with time, see Chapter 1.

Case detection and chemotherapy

There is no evidence that case detection and chemotherapy reduced transmission, although this was claimed in the reviewed papers for two areas with supposedly no economic improvement and no systematic BCG vaccination (French Polynesia between 1946-1966, Ethiopia). Clearance of initial backlogs in case detection may also have contributed to the CDR declines in these areas (Ethiopia: see (*4*)). The literature review does not demonstrate a general acceleration of existing declines in CDR following the replacement of dapsone monotherapy by MDT. Such an impact is still not visible when the CDR time series from the review are augmented with more recent data.

Interaction with tuberculosis

We refrained from exploring a possible protective effect against leprosy of tuberculosis infection and/or disease, because the interpretation of leprosy trends alone is already difficult due to issues such as continuity of data collection and of control activities (see Chapters 2 and 5).

Reductions in case detection efforts

These might lead to reductions in case detection, but also to later detection of patients and thus to increases in transmission. In the literature review, we did not find indications for associations between overall declines in CDR and decreases in leprosy control efforts, with one possible exception (Bhutan).

CDR trends since 1985

Case detection efforts were intensified in the 1990s, see Chapter 3. This is the most likely reason for the increases in CDR as observed in the majority of countries addressed in Chapter 3, since it is hard to imagine that leprosy transmission increased simultaneously in all these countries. Nonetheless, it has been suggested that increased transmission may have played a role in the Brazilian increase in CDR which persisted over a period of almost three decades, because the main operational changes are said to have occurred after 1986 (Chapter 2).

Question 3

To what extent have isolation of patients and socio-economic improvement contributed to the disappearance of leprosy from Norway?

Answer

The with SIMLEP estimated contribution of isolation of patients in hospitals to the total decline in the Norwegian case detection rate ranges from 3% to 60%; the corresponding contributions of the competing explanation socio-economic improvement are 95% and 34%, respectively. The joint effect of these explanations is larger than the sum of the simulated separate effects.

Comment

The case detection rate of leprosy in Norway steadily declined between 1856 and 1920, while detection efforts were rather stable. The decline took place long before effective chemotherapy became available, and in absence of BCG vaccination. It has been suggested that the following factors may have contributed to the decline: isolation of patients, socio-economic improvement, selective emigration and interaction with tuberculosis (5).

Chapter 5 presents an analysis of the relative contributions of isolation of patients in hospitals versus socio-economic improvement to the decline of leprosy in Norway with the leprosy simulation model SIMLEP. The Norwegian trend in leprosy case detection was reproduced adequately, and equally well with contrasting assumptions on uncertain aspects of leprosy epidemiology which govern the impact of control on leprosy transmission (see under question 4). The estimated contribution of hospital isolation to the decline ranged from 3% to 60%, depending on the assumptions made regarding transmission (corresponding contribution of socio-economic improvement: from 95% to 34%).

We investigated the relative contributions of hospital isolation and socio-economic improvement on the decline. We could not assess the importance of the suggested alternative explanations – isolation of patients in their own homes, selective emigration of individuals at increased risk and/or those incubating, and possible interaction with tuberculosis – due to lack of data. SIMLEP has also no provisions for studying an interaction between leprosy and tuberculosis. Thus, the predicted contributions of hospital isolation and socio-economic improvement may overestimate the true contributions. Non-selective emigration did not influence the predictions for hospital isolation and socio-economic improvement.

Inspired by an earlier geographical analysis of declines in the incidence (5), we hoped to be able to further narrow down the uncertainty regarding the role that hospital isolation may have played. Within Norway, geographical differences existed regarding the start and the rates of the decline in the incidence on the one hand, and the 'degree of isolation' on the other (incidence refers to onset of disease). This degree was introduced as a measure of how often and long patients were hospitalised. The earlier analysis showed a strong positive association between this degree and the relative fall in the incidence rate in the next decade in the different Norwegian counties during 1856-1875, but not during 1881-1910. Unfortunately, the interpretation of this association is not straightforward, for several reasons. Firstly, both the degree of isolation and the relative decline in incidence rates increased over time. Secondly, the central office of the National Leprosy Registry of Norway was located in the southern region of coastal counties where leprosy was predominant, in the city of Bergen which also accommodated a research hospital that was completed in 1849. This complicates the interpretation of incidence trends: the decline in incidence rate was right from the founding of the registry in 1856 in the southern region, but started only around 1870 in the middle and northern region. Thirdly, geographical

differences in start and pace of socio-economic improvement can also not be excluded. Due to these complications, we refrained from a geographic analysis of the Norwegian trend data with SIMLEP.

Question 4

Which uncertain aspects of leprosy epidemiology contribute most to the uncertainty about the impact of leprosy control on transmission?

Answer

In our studies, the most important uncertain aspects are whether contagiousness builds up during the incubation period, the importance of close contact in transmission and the speed at which close contacts become infected.

Comment

In the analysis of the Norwegian data, we started with a very simple model, which was refined step by step until an adequate fit of the age-specific trend data was reached (Chapter 5). The resulting model neither assumed contagiousness during the incubation period, nor decreases in a patient's transmission opportunities over time due to exhaustion of susceptibles. Both possibilities are not implausible. The first because there is no reason why the shedding of bacilli would start only at the onset of the first clinical sign of leprosy. The second because close contacts of leprosy patients may be infected rapidly, and because close contact – either in the own household or through neighbours and social contacts – may be important for transmission. We explored these possibilities because both transmission during the incubation period and rapid transmission limit the fraction of transmission that can be prevented by leprosy control.

The quality of the fit of the Norwegian data hardly changed when contagiousness was assumed to build up during the incubation period, or when transmission opportunities were assumed to decrease at different rates. However, these assumptions did have a large impact on the estimated contribution of hospital isolation to the Norwegian decline: it decreased from 60% to 36% when build-up was assumed, and further down to 17%, 9% and 3% upon assuming half-value times of transmission opportunities for patients of 8, 4 and 2 years, respectively.

A third assumption that we expected to affect the contribution of isolation is the length of the incubation period: the contribution should increase with shorter incubation periods because these imply shorter turnaround times of the transmission cycle. However, relatively small reductions in the length of the incubation period already led to a worsening of the quality of the fit of the trend data: the shorter turnaround time caused the simulated declines in Norwegian case detection during the first few decades to be too fast.

The scenario analysis of future trends in the transmission and incidence of leprosy from Chapter 6 builds on the Norwegian findings. The trend in case detection rate in major endemic countries during 1985-1998 was fitted using various SIMLEP models, and

incidence rates were projected up to 2020. The same alternative assumptions regarding build-up of contagiousness and decrease of transmission opportunities were made as in the Norwegian study, and these influenced heavily the incidence predictions. Other uncertain aspects which were varied in a sensitivity analysis hardly mattered, except for the length of the incubation period and the trend in detection delay up to 1998. Shortening of the incubation period gave a similar effect as in the Norwegian study: the predicted declines in incidence rates during 2000-2020 were faster for the various models considered, but less models gave a good fit to the historical trend data. Assuming larger reductions in the detection delay compared to the baseline trend had the same effect (the detection delay was assumed to decrease over time, and was always two years on average from 1998 onwards).

Among the other uncertain aspects that were addressed are the fraction of new infections progressing to disease, the type distribution of new cases, the self-healing rate for self-healing disease, the duration of dapsone monotherapy and relapse rates after dapsone. The possibility that cases who eventually self-heal are contagious too was not explored: we judge this issue to be much less important for assessing the impact of interventions on transmission than the moment (also before onset of disease?) at which transmission takes place. A second possibility that was ignored in the scenario analysis of Chapter 6 is that individuals first go through an episode of non-contagious disease before developing contagious disease ('downgrading'). Further simulations showed that this assumption often resulted in conflicts with the 1985-1998 case detection trend for the major endemic countries.

The introductory Chapter 1 of this thesis already indicated that knowledge on the process of leprosy transmission is still very limited. In our studies, we adhered to the common notion that leprosy is transmitted predominantly within the human population. But we did not explore all hypotheses on possible human sources of leprosy transmission. For instance, we ignored the possibility of an important role for individuals with infections that self-heal without any manifestation of disease, but only after a transient period of nasal excretion. This hypothesis further underlines that three key questions need to be answered in order to understand whether and how leprosy transmission can be reduced. These questions are: (1) 'is leprosy predominantly transmitted to close contacts or to the general population?', (2) 'at what rate do contagious individuals transmit *M. leprae* to susceptible individuals (speed of transmission)?' (3) 'how much do individuals without signs of leprosy contribute to transmission?'.

Compared to other diseases, the potential yield of a simulation modelling approach for leprosy was limited. Our approach has improved the insight in the impact of interventions for leprosy, we have identified the gaps in knowledge about leprosy that matter most, and we have shown how much these gaps matter: the uncertainty about the impact of leprosy control remains high (see questions 3 and 5). Due to its group-compartmental design, our present modelling framework SIMLEP does not allow for detailed description and simulation of how leprosy spreads within populations (see

Chapters 1 and 4). Application of a leprosy simulation model which is capable of this would enable further narrowing down of the uncertainty about the impact of leprosy control, but so far, we have not identified datasets that provide sufficient information for developing, quantifying and validating such models.

In 2002, a large prospective field study was started into the role of close contact in the transmission of leprosy and effectiveness of chemoprophylaxis for close contacts of leprosy patients ('COLEP: a prospective (sero-)epidemiological study on contact transmission and chemoprophylaxis in leprosy') (6). The study is unique in that it distinguishes various levels of closeness of contact to a leprosy patient, whereas it also involves an extensive serological component. Contacts are classified according to both physical distance – those living under the same roof and/or eating from the same kitchen, neighbours, neighbours of neighbours, social contacts – and genetic distance. Thus, the study is expected to provide a wealth of data regarding patterns according to which leprosy spreads in a population. Along with this trial, our research group will develop a micro-simulation model for leprosy transmission. In a micro-simulation approach, relevant aspects of life histories of individual human beings are simulated. The micro-simulation approach allows for keeping track of whether an individual is a contact of a leprosy patient and his/her physical and genetic distance to the patient. Through this approach, we hope to further improve knowledge about patterns of leprosy transmission in populations and to further narrow down the uncertainty about the impact of present day control on time trends in transmission. This approach will also allow for evaluating the impact of alternative control policies targeted at close contacts of leprosy patients (chemoprophylaxis, immunoprophylaxis) which receive increasing interest. This evaluation is not possible with SIMLEP, simply because it does not distinguish close contacts from the general population.

Question 5

What is the impact of present day control – case detection and chemotherapy, BCG vaccination – on the transmission of leprosy?

Answer

The impact of case detection and chemotherapy on transmission remains highly uncertain: our estimates range from hardly any impact at all up to a reduction in the incidence rate of leprosy of 10% per year. Under optimistic assumptions about efficacy and coverage, BCG enhances the predicted declines in incidence rates in the next two decades with a few percents. Overall, our estimates indicate that present day control will reduce leprosy incidence rates up to 2020 with in between 1% and 12% per year.

Comment

In the scenario analysis of future leprosy trends reported in Chapter 6, predicted declines in leprosy incidence had to be due to leprosy control. This is because the possibility of autonomous decreases in transmission, for instance due to socio-economic improvement

instead of control, was ignored. First, only case detection and chemotherapy was considered. In this case, the predicted annual decline in incidence rate between 2000 and 2020 varied from 2% to 8% with different assumptions regarding build-up of contagiousness and decrease of transmission opportunities (see under question 4). The range was from 5% to 10% when BCG vaccination was considered as well. These ranges are from 1% to 10% without BCG and from 3% to 12% with BCG, respectively, when other aspects of leprosy epidemiology and assumptions about leprosy control are varied in a sensitivity analysis (range without BCG not shown in Chapter 6). Thus, the overall range for the annual reduction in leprosy incidence rates is from 1% to 12%.

A reflection on the scenario analysis is required. Scenarios were fitted to the average historical trend in CDR over 1985-1998 for 14 major endemic countries before incidence projections were made (see question 1). The range from 1% to 12% is based on scenarios with good fits to this average CDR. Since the average CDR trend will only in some cases be representative for the trend in individual countries, the criterion for classifying fits as 'good' was not very strict: the annual change in CDR was allowed to differ 50% from the annual increase in the historical CDR trend. The historical CDR increased from 1.3 to 2.3 per 10,000 per year. Additional investigations showed that the predicted annual declines changed only slightly upon assuming different levels for the historical CDR trend. The CDR level for India, which dominates global detection, was quite stable during 1985-1998, averaging 5.7 per 10,000 per year. The predicted declines in incidence rate between 2000 and 2020 were slower when case detection rates were fitted to the stable Indian CDR. The assumptions on mean delay in case detection after the year 2000 and on efficacy and coverage of BCG vaccination were on the optimistic side, see also Chapter 6. These considerations support our estimate that present day control will reduce leprosy incidence rates up to 2020 with 1% to 12% per year.

Autonomous decreases in transmission will accelerate declines in transmission that are the consequence of leprosy control. Thus, annual declines in incidence rate that exceed 12% per year cannot be excluded. Declines in incidence rate or CDR by more than 12% per year have been reported for a number of areas/countries in Chapter 2 and in a review by Irgens (7), see Table 9.1. It is suggested that autonomous decreases due to socio-economic improvement have contributed to the declines in Weifang, Mainland Japan and Okinawa. The declines listed in Table 9.1 have to be interpreted with caution. Pronounced declines in the first years of the observation period influenced the overall rates of decline in Shandong and Weifang (which is part of Shandong), and in Uele Region and Ndi Oji Abam. These initial declines may be due to reduction of backlogs in the detection of leprosy patients following the initiation of control activities, and reduction of false-positives in case ascertainment may have been a contributing factor in Uele Region. The annual decline in CDR in Uele Region was only 5% per year during 1980-1988, versus 19% for 1975-1988 as a whole. The initial CDR in Ndi Oji Abam, which had a population of only 3,000 individuals, was extremely high: 13.2 per 1,000 per year. CDRs were already below one per 100,000 per year at the start of the observation

Table 9.1 Areas and countries with average annual declines in incidence rate or case detection rate of more than 12% per year.

Area / country (*reference no.*)	Period of decline	Average annual decline (%)
China, Shandong Province (*8*)	1958 – 1979	14%[a]
China, Weifang Prefecture (*9*)[b]	1955 – 1993	13%
Congo, Uele Region (*10, 11*)[b]	1975 – 1988	19%
Japan, Mainland (*12*)	1950 – 1980	13%
Japan, Okinawa (*13*)	1967 – 1980	17%
Mexico (*14*)[b]	1980 – 1989	13%
Nigeria, Ndi Oji Abam (*15*)	1941/1945 – 1952/1956	16%

[a] Calculated on the basis of rates of leprosy incidence, which denotes onset of disease as reported by patients.
[b] See also Chapter 2.

period in Mainland Japan and Mexico, and the decline in incidence rate (which refers to onset of disease) accelerated in Shandong Province once it reached one per 100,000 per year.

Question 6

What is the relationship between the delay in case detection and the impairment status of patients at the time of detection, and how does the impairment status change during treatment and after release from treatment?

Answer

The prevalence of impairment caused by leprosy in newly detected patients increases strongly with longer delays in case detection. Newly detected patients who are initially free from impairment may develop impairments over time, and the impairment status of impaired patients may both improve and worsen after the time of detection. Still, the impairment status of patients at the time of detection is the most important determinant for future impairment.

Comment

Data from a cohort of newly detected patients from a long-term prospective study into the effectiveness of MDT was analysed (ALERT's AMFES study in Ethiopia). The prevalence of any impairment in new patients increased continuously from 36% for delays of less than one year to 81% for delays of four years or more, and the prevalence of WHO grade 2 impairment increased similarly from 10% to 43% (Chapter 7).

About half of the patients were detected with impairment. Of those initially impaired, around 20% had recovered at release from treatment. A similar percentage of this group with impairment at detection was free from impairment at follow-up (24-48 months after

release from treatment). Of those initially free from impairment, 11% did have impairment at release from treatment, and 14% at the time of follow-up (the latter result was not shown in Chapter 8). Looking backwards, about 90% of both those with impairment at release from treatment and those with impairment at follow-up already had impairment at the time of detection. The dynamics of existing impairment were less favourable after release from treatment than before, but important changes over time in the cohort's distribution of the EHF-score – which is the sum of the WHO impairment grades for eyes, hands and feet, see Chapter 1 – did not occur.

The key results from other studies were quite similar, even though these studies differ considerably in the percentage of patients that already had impairment at the time of detection. Two studies confirmed the found strong positive association between the detection delay and impairment in new patients, see Chapter 7. Studies from Bangladesh, Malawi, Nepal and Thailand addressed dynamics of impairment, see Chapter 8. Patients were reassessed at release from treatment, except in Nepal where the reported reassessment took place two years after detection. Further analysis of these studies shows that more than 80% of patients with impairment at the time of the reassessment already had impairment at the time of detection, except for one study (more than 70%). The overall percentage of patients with impairment hardly changed between the times of detection and reassessment in Bangladesh and Thailand, and decreased from 56% to 45% in Nepal. Comparison was not possible for Malawi. The studies do not enable comparison of the impairment status at the start of treatment and several years after release from treatment.

9.2 Impairment caused by leprosy: an exploration of the future

Leprosy is a public health problem because it causes impairment and disability. Demands for care are driven by the number of individuals with impairment. Estimating prevalence of impairment was not the subject of any of the previous chapters. Because of the importance of this topic, we below present scenarios for global prevalences of impairment up to 2020, which are derived by calculating the survival of both existing and new impaired cases. Results are in terms of WHO grade 2 impairment, because control programmes only routinely report the percentage of newly detected cases having grade 2 (see Chapter 1; we refer to the grades as 'impairment grades' instead of 'disability grades').

The estimates for leprosy incidence rates and CDRs from section 9.1 are used for specifying three scenarios of future declines in incidence rates beyond 2000: a worst case scenario (constant annual decline: 1%), a medium case scenario (6%) and a best case scenario (12%). Table 9.2 shows the number of cases that will be detected globally in 2010 and 2020, under the assumption that the annual declines in CDR and incidence rate will be equal. The global CDR for the period 1994-2000 is used as initial CDR, because CDRs in the late 1990s were elevated (see Chapter 3). In the worst case scenario, annual case detection hardly changes: population growth and the assumed decline in CDR

Table 9.2 Scenarios for case detection corresponding to a 1% annual decline in the global incidence rate of leprosy beyond the year 2000 (worst case scenario), a 6% annual decline (medium case scenario), and a 12% annual decline (best case scenario).

	No. of cases detected (hundred thousands)		Cumulative no. of cases detected in a 10-year time period (hundred thousands)	
	2010	2020	2001-2010	2011-2020
Worst case scenario	6.9	6.9	69	69
Medium case scenario	4.1	2.5	52	31
Best case scenario	2.1	0.7	38	12

compensate each other. In the medium case, still about 250,000 new cases will be detected in the year 2020 (65% less than in the worst case). The best case scenario shows a more than ten-fold reduction in case detection between 2000 and 2020: the global case detection has fallen to about 65,000 cases (91% less than in the worst case). Still, even in this scenario, nearly four million cases will be detected up to 2010, and over one million cases between 2010 and 2020.

The next step is to calculate the numbers of future new cases that will present with WHO grade 2 impairment. To perform this calculation, we assume that 6% of new cases detected during each of the years 2001 to 2020 will have grade 2. This 6% is fairly optimistic; it is the percentage of new cases with grade 2 that was reported by the Bangladesh Acute Nerve Damage Study (BANDS) (*16*). BANDS is conducted within a high quality control programme, and the percentage with grade 2 was always at least 7% in the impairment and disability studies reviewed by us (see question 6).

Results for the 6% WHO grade 2 assumption are as follows (Table 9.3). In the worst case scenario, global annual detection of new cases with grade 2 is about constant at 42,000 cases per year, resulting in 830,000 new cases with grade 2 for 2001-2020 as a whole. In the medium case scenario, the annual number of newly detected cases with grade 2 will have fallen to 15,000 cases by the year 2020, but the cumulative detection over 2001-2020 still equals half a million cases. In the best case scenario, 4,000 new cases will be detected with grade 2 in 2020, and 300,000 cases over 2001-2020.

The demands for care are determined by the prevalence of impairment, i.e. the number of individuals living with impairment. For a given point in time, we estimate this prevalence as the number of new cases that were detected with WHO grade 2 before that point, and survived up to that point. Worldwide, about 680,000 new cases were detected with grade 2 during the period 1985-2000. We use backward extrapolation to estimate numbers of new cases with grade 2 up to 1985. Table 9.3 provides the required estimates for the global detection of new cases with grade 2 beyond the year 2000.

Table 9.3 Estimated global detection of new patients presenting with WHO grade 2 impairment in the years 2001-2020, according to three scenarios for the annual decline in the global incidence rate and CDR of leprosy beyond the year 2000.

	No. of grade 2 cases detected (hundred thousands) [a]		Cumulative no. of grade 2 cases detected in a 10-year time period (hundred thousands)	
	2010	2020	2001-2010	2011-2020
Worst case scenario	0.42	0.42	4.1	4.2
Medium case scenario	0.25	0.15	3.1	1.9
Best case scenario	0.13	0.04	2.3	0.7

[a] Calculated on the basis of projections of the size of the world population (17), scenarios for the annual decline in CDR beyond 2000 (see main text and Table 9.2), and 6% WHO grade 2 impairment in cases detected during 2001-2020.

In the survival calculations, we assume that there is no excess mortality due to leprosy: age-specific death rates for the general population of Bangladesh for the year 1994 are used (18). The age distribution of new cases presenting with WHO grade 2 in the control programme of the Danish Bangladesh Leprosy Mission in Bangladesh is used to calculated ages of the impaired cases at the time of their detection (DBLM; unpublished data over 1986-1990). The mean age at detection of new cases with WHO grade 2 in DBLM was 39 years, and the remaining life expectancy at this age is 31 years.

In our calculations, 1.3 million individuals were alive with WHO grade 2 impairment by the end of the year 2000. This is within the wide range that was estimated by WHO in the 1990s (1-2 million, see Chapter 1). Due to 72% survival and its size, the group from 2000 contributes more than 70% to the global WHO grade 2 prevalence in 2010 in all three scenarios (Table 9.4). About half of this group survives up to 2020 (0.6 million individuals). The situation per scenario varies somewhat more in this year. In the worst case scenario, cases detected during 2001-2020 account for about half of the global WHO grade 2 prevalence of 1.4 million (this figure is slightly higher than in 2000, which is due to growth of the world population). The contributions are about 40% and 30% for the medium and best case scenario, respectively. In the best case scenario, the global WHO grade 2 prevalence in 2020 is still about 0.9 million, despite of the sharp fall in the detection of new cases with WHO grade 2 to only 4,000 cases in this year.

To our knowledge, this is the first time that projections of future impairment are presented, and our projections are rather crude. We assumed stability in the impairment status of patients, inspired by studies comparing impairment at diagnosis and release from treatment (question 6). However, the follow-up period in these studies was not long, and individuals with anaesthetic nerves (grade 1 impairment) remain at risk for developing visible deformities or damage (grade 2). The frequency of the reverse, permanent improvement of WHO grade 2 impairment after release from treatment, will probably be

Table 9.4 Global prevalence of WHO grade 2 impairment in 2010 and 2020, according to three scenarios for the annual decline in the global incidence rate and CDR of leprosy during 2000-2020.

	Prevalence of WHO grade 2 impairment (hundred thousands) [a]	
	2010	2020
Resulting from cases from before 1985 [b]		
Each scenario	5	2
Resulting from cases detected during 1985-2000 [c]		
Each scenario	5	4
Resulting from cases detected during 2001-2020		
Worst case scenario	4	7
Medium case scenario	3	4
Best case scenario	2	2
Total prevalence		
Worst case scenario	14	14
Medium case scenario	13	11
Best case scenario	12	9

[a] Calculated as the number of new cases detected previously with WHO grade 2, and surviving until the end of 2010 and 2020, respectively.

[b] For years before 1985, the number of new cases with WHO grade 2 is estimated by multiplying the world population size with the estimated global case detection rate for 1985 and with the percentage of new patients detected with grade 2 in the top 32 endemic countries in 1985 (9.6%) (*19*). The global case detection rate for 1985 is estimated by dividing the number of new patients detected in 1985 in the top 32 endemic countries by the 1985 world population size (see Chapter 3).

[c] The estimated number of new cases detected during 1985-2000 with WHO grade 2 impairment is 680,000. This estimate is the sum of the reported number of new cases with WHO grade 2 in the top 32 endemic countries during 1985-1996 (*19*), and the estimated number of new cases detected globally with WHO grade 2 during 1997-2000. The latter estimation is based on the total number of new cases detected globally in the years 1997-2000 (*20*) and percentages of new patients with WHO grade 2 impairment that were reported in the years 1996 and 2000 (*20, 21*).

lower. In addition, awareness and detection efforts may decrease when leprosy becomes less frequent, leading to later detection and more impairment at the time of detection. Thus, we may have underestimated future prevalences of WHO grade 2 impairment. The opposite is also possible, because we assumed that there is no excess mortality in those with WHO grade 2 impairment. Although leprosy is in principle non-lethal, excess mortality may occur due to inappropriate care. We used a lifetable for the year 1994, which implies that we overestimated survival up to 1994, and underestimated survival afterwards. However, these considerations will not alter the main conclusion: the demands for care posed by individuals with impairment caused by leprosy will at best only decrease slowly.

9.3 Conclusions and recommendations

Conclusions

- To date, there is no general decline in annual numbers of leprosy patients detected in major endemic countries.

- The impact of chemotherapy and BCG vaccination on trends in the transmission and incidence of leprosy is highly uncertain. Chemotherapy, BCG and other factors that may have contributed to downward trends in the past cannot be disentangled.

- This uncertainty is largely due to three unresolved questions regarding infectiousness and transmission:
  - is leprosy predominantly transmitted to close contacts or to the general population?
  - at what rate do infectious individuals transmit *M. leprae* to susceptible individuals?
  - to which extent do individuals without signs of leprosy contribute to transmission?

- The prevalence of impairment caused by leprosy increases strongly with longer delays between onset of signs and diagnosis.

- A patient's impairment status at diagnosis is the most important determinant for impairment in the future.

- The global prevalence of WHO grade 2 impairment will only decrease very slowly in the foreseeable future.

Recommendations

- Chemotherapy based control must be sustained at the present level for at least the next ten years, after which leprosy trends should be critically reappraised in order to judge whether control efforts can be relaxed.

- Leprosy control programmes should place emphasis on reducing delays in case detection, because early detection is essential for prevention of impairment and disability and for prevention of transmission. Reduction of delays requires more knowledge on health seeking behaviour. Improved knowledge will enable the development of new methods that enhance earlier case detection.

- A research strategy that combines different disciplines of leprosy research (epidemiology, microbiology, immunology, genetics, simulation modelling) should be developed to address the unresolved questions regarding infectiousness and transmission.

- Simulation modelling has a role in investigating patterns of transmission of *M. leprae* in populations in more detail, and in addressing the potential impact of strategies of primary prevention (chemoprophylaxis, immunoprophylaxis) targeted at close

contacts of leprosy patients. Models should be developed and used alongside prospective epidemiological field studies, enabling in depth analysis and interpretation of results.

9.4 References

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Summary

This thesis addresses the impact of leprosy control on the occurrence of leprosy and its associated impairments.

Chapter 1 introduces leprosy, an infectious disease. Its manifestations vary widely: from mild self-healing forms to chronic and destructive disease. Knowledge regarding transmission of the leprosy bacterium *Mycobacterium leprae* is limited. For instance, it is unknown to what extent individuals incubating for disease contribute to transmission. Leprosy is a public health problem because it may cause nerve function impairment, leading to secondary complications of eyes, hands and feet. Disability, handicap and social stigma are ultimate consequences. Activities to prevent impairment and disability are very important. Early detection of patients followed by chemotherapy is the mainstay of leprosy control. The introduction of highly bactericidal multidrug therapy (MDT) in the 1980s was a strong impetus for control programmes. However, evidence for an impact of MDT on transmission and incidence is still lacking.

Chapter 2 is a review of publications that provide time series for case detection with a span of at least ten years, for 16 areas and countries in different parts of the world. Data did not extend beyond 1993. Case detection rates (CDRs) decreased in most areas and countries. The data did not allow for disentanglement of factors which may have contributed to the declines. The declines could not be attributed to relaxation of control activities or changes in criteria for the diagnosis of leprosy. There was no general acceleration of the declines after the introduction of MDT. The long incubation period of leprosy may have masked a possible influence of MDT.

Publication bias towards high-quality control programmes and downward trends may have influenced the review. This is supported by the findings of **Chapter 3**, which describes case detection at regional and national levels using country statistics. Complete time series for case detection could be constructed for 1985-1998 for 33 endemic countries cumulatively (top 33), and for 14 individual countries in different WHO Regions (top 14). Global case detection was only available for 1994-2000.

The top 33 had a nearly 100% share in global case detection. India accounted for at least 75% of detection in the top 33 throughout 1985-1998, and the other top 14 countries for at least 75% of remaining detection. The CDRs were rather stable or increased for 10/14 countries. The Indian CDR very slowly decreased up to 1996 and subsequently increased. A decreasing tendency in CDR was observed for 4/14 countries. Case detection for the top 33 minus India increased gradually during 1985-1998, overall almost doubling. Global case detection equalled 560,000 cases in 1994, peaked at 800,000 in 1998, and was 720,000 in 2000. In conclusion, there is no general decline in case detection so far. Detailed

information is lacking, but control programmes were intensified in many countries in the 1990s. Underlying trends in leprosy transmission and incidence could not be clarified.

We developed the epidemiological model SIMLEP to investigate the impact of leprosy control on transmission and incidence (**Chapter 4**). SIMLEP has a group-compartmental design. The compartments reflect health states regarding leprosy infection and disease. Changes in these states are determined by epidemiological parameters. The parameter values and a set of mathematical equations determine how an epidemiological situation, i.e. the fractions of the total population with the various health states, evolves over time. SIMLEP considers two interventions: early case detection followed by chemotherapy, and bacille Calmette-Guérin (BCG) vaccination of infants. BCG is part of the Expanded Programme on Immunization (EPI) as a preventive measure against tuberculosis, and may influence leprosy trends. SIMLEP is age specific, and does not simulate impairment and disability.

SIMLEP was used to analyse the downward trend of leprosy in Norway (**Chapter 5**). Leprosy was endemic in 1850, and had virtually disappeared by 1920. A patient database documents the declining trend extremely well. The Norwegian health authorities implemented a policy of isolation of patients in hospitals, and Norway experienced continuous economic growth during the period of the decline. SIMLEP reproduced the declining trend in case detection adequately, and equally well with contrasting assumptions regarding build-up of contagiousness during the incubation period of leprosy and decreasing transmission opportunities of patients. These opportunities may decrease because to a certain extent, close contact may be a prerequisite for transmission, and close contacts of a leprosy patient may become infected rapidly. For each set of assumptions (scenario), reproducing the declining trend required postulating an autonomous decrease in transmission, reflecting socio-economic improvement. The simulated contribution of hospital isolation to the decline ranged from 3% to 67%, with socio-economic improvement as competing explanation.

Building on the Norway study, a scenario analysis of future trends in leprosy incidence was conducted (**Chapter 6**). A historical trend in CDR was fitted for each scenario, and incidence was projected up to 2020. For the historical CDRs, the average of the CDRs of the 'top 14' endemic countries for 1985-1998 of Chapter 3 was used. A strategy of early case detection and chemotherapy lies at the basis of all simulated scenarios. A gradual reduction in the delay between onset of disease and start of treatment, or 'detection delay', to two years from 1998 onwards was assumed, reflecting that leprosy control activities were intensified. Dapsone monotherapy was replaced by MDT in 1990. The scenarios differed on the same aspects as in the Norway study.

The incidence decreased beyond 2000 in all scenarios due to the shortened detection delay, but also because MDT has a very low relapse rate. Without infant BCG vaccination, the predicted annual decline in incidence rate beyond 2000 ranged from 2% − 8% for the scenarios with a good fit to the historical CDR trend. The annual decline was a few percent higher with favourable assumptions about protection and coverage of

BCG: from 4% – 10%. Other uncertain aspects of leprosy epidemiology were varied in a sensitivity analysis, leading to an overall range in the annual decline from 1% – 12% (for the 1% lower bound, see Chapter 9). Relaxation of control beyond 2005 through longer detection delays slowed down the declines. Thus, early case detection and MDT will reduce transmission, but the decline may be slow. Relaxation of control in the near future is unjustified, and a long-term perspective to leprosy control should be adopted.

The issue of impairment caused by leprosy was addressed using data from a prospective study of a cohort of Ethiopian patients (AMFES). A grade of 0-2 was assigned to each eye, hand and foot to measure severity of impairment. The maximum and sum of the six grades of a patient are below referred to as the 'WHO impairment grade' and 'EHF-score', respectively.

The prevalence of impairment in new patients increased strongly with longer delays in case detection: from 36% for delays of less than one year to 81% for delays of four years or more (**Chapter 7**). The increase was from 10% to 43% for WHO grade 2 impairment. The importance of the detection delay as risk factor for any impairment and WHO grade 2 impairment was confirmed by multivariate logistic regression. The dynamics of existing impairment were less favourable after release from MDT treatment (rft) than before (**Chapter 8**). Important changes over time in the EHF-score distribution of the cohort as a whole did not occur. About 90% of patients with impairment at rft and patients with impairment at follow-up (24-48 months after rft) already had impairment at the time of detection. Thus, the impairment status at the time of detection is by far the most important determinant for future impairment.

In the Discussion of this thesis (**Chapter 9**), we provide estimates for the number of new patients that will present with impairment in the future globally, and for the future global prevalence of impairment. The explorations build on the scenario analysis of Chapter 6. Three scenarios for declines in incidence rate beyond 2000 are considered: a worst case scenario (1% annual decline), a medium case scenario (6%) and a best case scenario (12%). Under the assumption that 6% of newly detected cases will have WHO grade 2 impairment, we predict that cumulatively, 830,000 new cases will be detected with WHO grade 2 during 2001-2020 in the worst case scenario, and 500,000 and 300,000 in the medium and best case scenario, respectively.

Future prevalences are predicted on the basis of survival calculations for existing and new impaired cases using age-specific death rates. Excess mortality for leprosy is not assumed, since leprosy is in principle non-lethal. In the literature, it is reported that during 1985-1998 worldwide about 680,000 newly detected cases presented with WHO grade 2 impairment. Backward extrapolation is used to obtain estimates for the period before 1985. According to the survival calculations, the global prevalence of WHO grade 2 impairment by the end of 2000 was 1.3 million. In the worst case scenario, the predicted global prevalence for 2020 is 1.4 million. The predictions are 1.1 million and 0.9 million for the medium and best case scenario, respectively. These results indicate that at best, the demands for care posed by individuals with impairment will only decrease slowly.

The conclusions and recommendations that follow from the research for this thesis are formulated in the Discussion chapter (**Chapter 9**), and are summarized below.

Conclusions

- To date, there is no general decline in annual numbers of leprosy patients detected in major endemic countries.

- The impact of chemotherapy and BCG vaccination on trends in the transmission and incidence of leprosy is highly uncertain.

- This uncertainty is largely due to three unresolved questions regarding infectiousness and transmission:
  - is leprosy predominantly transmitted to close contacts or to the general population?
  - at what rate do infectious individuals transmit *M. leprae* to susceptible individuals?
  - to which extent do individuals without signs of leprosy contribute to transmission?

- The prevalence of impairment caused by leprosy increases strongly with longer delays between onset of signs and diagnosis.

- A patient's impairment status at diagnosis is the most important determinant for impairment in the future.

- The global prevalence of WHO grade 2 impairment will only decrease very slowly in the foreseeable future.

Recommendations

- Chemotherapy based control must be sustained at the present level for at least the next ten years, after which leprosy trends should be critically reappraised in order to judge whether control efforts can be relaxed.

- Leprosy control programmes should place emphasis on reducing delays in case detection, because early detection is essential for prevention of impairment and disability and for prevention of transmission.

- A research strategy that combines different disciplines of leprosy research should be developed to address the unresolved questions regarding infectiousness and transmission.

- Simulation modelling has a role in investigating patterns of transmission of *M. leprae* in populations in more detail, and in addressing the potential impact of strategies of primary prevention targeted at close contacts of leprosy patients.

Samenvatting

Dit proefschrift behandelt de invloed van leprabestrijding op het vóórkomen van lepra en de met lepra samenhangende zenuwbeschadigingen en gebreken.

Het inleidende **Hoofdstuk 1** geeft algemene informatie over de besmettelijke ziekte lepra. Lepra kent een breed scala van verschijningsvormen, van milde en zelfgenezende vormen tot chronische en destructieve ziektebeelden. De kennis over transmissie van de leprabacterie *Mycbacterium leprae* is beperkt. Het is bijvoorbeeld onbekend hoe besmettelijk iemand is gedurende de incubatietijd. Lepra is een volksgezondheidprobleem omdat het zenuwen kan beschadigen, wat kan leiden tot secundaire complicaties in vooral de ogen, handen en voeten. Fysieke beperkingen, invaliditeit en sociaal stigma zijn de uiterste gevolgen. Activiteiten om zenuwbeschadigingen en fysieke beperkingen te voorkomen zijn dan ook een belangrijk onderdeel van bestrijdingsprogramma's. De pijler waarop leprabestrijding rust is vroege opsporing van patiënten, gevolgd door het geven van antibiotica (chemotherapie). De bestrijding kreeg rond 1980 een sterke impuls met het beschikbaar komen van een combinatie van effectieve antibiotica, in de vorm van multidrug therapie (MDT). Tot op heden is echter nog niet aangetoond dat MDT de transmissie van de bacterie en het ontstaan van nieuwe patiënten (incidentie) beïnvloedt.

Hoofdstuk 2 is een studie van publicaties die tijdreeksen van aantallen nieuw opgespoorde patiënten bevatten voor 16 gebieden en landen in verschillende delen van de wereld. De gegevens betroffen de periode vóór 1994. Het aantal opgespoorde patiënten per hoofd van de bevolking, de 'case detection rate' (CDR), nam af in de meeste gebieden en landen. De gegevens bleken het niet mogelijk te maken om de factoren te ontrafelen die bijgedragen kunnen hebben aan de afnames. Pogingen om leprapatiënten op te sporen waren niet minder geworden, en de afnames in CDR konden ook niet worden toegeschreven aan veranderingen in de criteria voor de diagnose van lepra. Er was geen algehele versnelling in de afnames na de introductie van MDT. De lange incubatietijd van lepra kan een mogelijke invloed van MDT aan het zicht hebben onttrokken.

De studie kan hebben geleden onder publicatiebias: gegevens van goede bestrijdings-programma's en gunstige trends zullen eerder gerapporteerd worden. De bevindingen van **Hoofdstuk 3** wijzen in deze richting. In dat hoofdstuk worden trends in de opsporing op regionale en nationale niveaus beschreven aan de hand van op jaarbasis gerapporteerde landelijke gegevens. Tijdreeksen konden worden geconstrueerd voor 1985-1998 voor 33 endemische landen tezamen (top 33), en voor 14 individuele landen in verschillende WHO Regio's (top 14). Over de opsporing op wereldniveau waren alleen gegevens beschikbaar voor 1994-2000.

Van de wereldwijd opgespoorde patiënten kwam bijna 100% uit landen die tot de top 33 behoorden. Gedurende de gehele periode 1985-1998 werd minstens 75% van de in de top 33 opgespoorde patiënten ontdekt in India. De andere top 14 landen namen minstens

75% van het overblijvende deel voor hun rekening. De CDRs waren vrij stabiel of namen toe voor 10/14 landen. De Indiase CDR daalde heel langzaam tot 1996 en nam vervolgens weer toe. De CDR liet een neergaande tendens zien in 4/14 landen. Er was in de periode 1985-1998 bijna sprake van een verdubbeling van het aantal opgespoorde patiënten in de top 33 minus India. De toename was geleidelijk. De wereldwijde opsporing besloeg 560.000 patiënten in 1994, piekte tot 800.000 in 1998, en was 720.000 patiënten in 2000. Er is dus geen algemene afname in het aantal opgespoorde leprapatiënten. Na 1990 werd de leprabestrijding in veel landen geïntensiveerd. Gedetailleerde informatie hierover is echter niet beschikbaar. Verheldering van onderliggende trends in de transmissie en incidentie van lepra was niet mogelijk.

Om de invloed van leprabestrijding op de transmissie en incidentie te onderzoeken ontwierpen wij het epidemiologische simulatiemodel SIMLEP (**Hoofdstuk 4**). SIMLEP is een groeps-compartimenten model. De compartimenten representeren stadia van infectie en ziekte. Epidemiologische parameters bepalen de stadiaveranderingen. De parameterwaarden en een stelsel van wiskundige vergelijkingen bepalen hoe een epidemiologische situatie, d.w.z. de fracties van de totale bevolking in ieder stadium, verandert over de tijd. In SIMLEP worden twee controlemaatregelen beschouwd: vroege opsporing gevolgd door chemotherapie, en bacille Calmette-Guérin (BCG) vaccinatie van pasgeborenen. BCG is opgenomen in het 'Expanded Programme on Immunization' (EPI) om tuberculose tegen te gaan, en zou ook het vóórkomen van lepra kunnen beïnvloeden.

De neergaande Noorse lepratrend werd geanalyseerd met SIMLEP (**Hoofdstuk 5**). Lepra was endemisch in Noorwegen in 1850, en was vrijwel verdwenen in 1920. De daling is zeer goed gedocumenteerd in een electronisch patiëntenbestand. De Noorse overheid voerde een beleid waarbij patiënten werden geïsoleerd in ziekenhuizen. Voorts groeide de Noorse economie onafgebroken in de periode dat lepra afnam. Met SIMLEP kon de neergaande trend in het aantal opgespoorde leprapatiënten per jaar adequaat worden nagebootst. De rol die het Noorse isolatiebeleid heeft gespeeld bleef echter onzeker. De neergaande trend kon namelijk even goed worden nagebootst met tegenovergestelde aannames met betrekking tot de opbouw van besmettelijkheid gedurende de incubatieperiode en afnemende mogelijkheden voor patiënten om anderen te besmetten. De mogelijkheid om anderen te besmetten neemt misschien af omdat nauw contact tussen mensen een vereiste kan zijn voor transmissie, en omdat de nabije contacten van een leprapatiënt snel besmet kunnen raken. Om de neergaande trend na te kunnen bootsen moest voor iedere combinatie van bovengenoemde aannames (scenario) een autonome afname in transmissie worden gepostuleerd. Hiermee wordt rekening gehouden met sociaal-economische vooruitgang. Voor de verschillende scenario's lag het gesimuleerde aandeel van het isolatiebeleid aan de verdwijning van lepra uit Noorwegen tussen 3% en 67%, met sociaal-economische vooruitgang als alternatieve verklaring voor deze verdwijning.

Voortbouwend op de Noorse studie werd een scenario-analyse uitgevoerd naar de toekomstige incidentie van lepra (**Hoofdstuk 6**). Een historische trend in CDR werd voor ieder scenario nagebootst, waarna de incidentie tot 2020 werd voorspeld. Voor de historische CDR werd het gemiddelde gebruikt van de CDRs van de 'top 14' endemische landen voor 1985-1998 van Hoofdstuk 3. Een strategie van vroege opsporing en het verstrekken van chemotherapie lag aan de basis van alle gesimuleerde scenario's. Een geleidelijke afname in de duur tussen aanvang van ziekte en start van behandeling (opsporingsduur) werd aangenomen, wat een weerspiegeling is van intensivering van de leprabestrijding. De veronderstelde opsporingsduur was twee jaar vanaf 1998. Dapsone monotherapie werd vervangen door MDT in 1990. De verschillen in aannames tussen de scenario's waren hetzelfde als in de Noorse studie.

De incidentie van lepra nam in alle scenario's af na 2000, vooral door de verkorte opsporingsduur. Een andere factor die bijdroeg was dat patiënten na MDT slechts zelden opnieuw ziek en besmettelijk worden. Zonder BCG vaccinatie van pasgeborenen varieerde de voorspelde afname in het jaarlijkse aantal nieuw ontstane patiënten per hoofd van de bevolking ('incidence rate') tussen 2% en 8% per jaar voor de scenario's waarvoor de historische CDR goed was nagebootst. Onder gunstige aannames over bescherming en dekkingsgraad van BCG was de jaarlijkse afname iets hoger: tussen 4% en 10%. In een gevoeligheidsanalyse werden andere onzekerheden in de epidemiologie van lepra gevarieerd, hetgeen leidde tot een uiteindelijke variatie in de jaarlijkse afname tussen 1% en 12%. Door langere opsporingsduren aan te nemen na 2005, wat ontspanning van de bestrijding weerspiegelt, vertraagden de afnames in incidentie. De conclusie is dat de transmissie van lepra inderdaad afneemt door vroege opsporing en MDT, maar ook dat de afname traag kan verlopen. De bestrijding mag in de nabije toekomst niet worden verslapt, en in de leprabestrijding moet worden vastgehouden aan een lange termijn visie.

De problematiek van zenuwbeschadiging en secundaire complicaties, tezamen hieronder aangeduid als 'gebreken', werd onderzocht met gegevens uit een prospectieve studie onder Ethiopische patiënten. Om de ernst van gebreken weer te geven kreeg ieder oog, en iedere hand en voet een score van 0, 1 of 2. Deze scores worden in dit proefschrift 'WHO impairment grades' genoemd. Volgens dit scoresysteem heeft een patiënt een gebrek als minstens één van de ogen, handen of voeten de score 1 of 2 heeft. Een 'WHO grade 2' wordt toegekend als minstens één van de ogen, handen of voeten de score 2 heeft. De som van de zes scores van ieder oog, iedere hand en iedere voet wordt de 'eye-hand-foot' (EHF) score genoemd.

De aanwezigheid van gebreken (prevalentie) in nieuw opgespoorde patiënten nam sterk toe met de opsporingsduur: bij een opsporingsduur korter dan een jaar had 36% van de patiënten gebreken en bij een opsporingsduur van vier jaar of meer was dit 81% (**Hoofdstuk 7**). Voor het hebben van WHO grade 2 waren deze percentages respectievelijk 10% en 43%. Het belang van de opsporingsduur voor het hebben van gebreken en het hebben van WHO grade 2 werd bevestigd door multivariate logistische regressie. Analyse van de EHF-score op verschillende momenten in de tijd liet zien dat

veranderingen in bestaande gebreken minder gunstig waren na voltooiing van MDT, wat 'slechts' de bacterie doodt, dan daarvoor. In de tijd deden zich echter geen belangrijke wijzigingen voor in de EHF-score verdeling van het cohort Ethiopische patiënten als geheel. Ongeveer 90% van de patiënten met gebreken bij voltooiing van MDT en van de patiënten met gebreken bij heronderzoek 24-48 maanden later had al gebreken op het moment van opsporing. Het hebben van gebreken op het moment van opsporing is dus verreweg de belangrijkste determinant voor het hebben van gebreken op een later moment.

In de Discussie (**Hoofdstuk 9**) maken wij een schatting van het aantal nieuwe patiënten dat in de toekomst zal worden opgespoord met gebreken, en de toekomstige wereldwijde prevalentie van patiënten met gebreken. Deze verkenning bouwt voort op de scenario-analyse van Hoofdstuk 6. Drie scenario's worden gebruikt voor de afname in het jaarlijkse aantal nieuw ontstane patiënten per hoofd van de bevolking ('incidence rate') na het jaar 2000: een 'worst case' scenario (1% jaarlijkse afname), een doorsnee scenario (6%) en een 'best case' scenario (12%). De aanname is dat 6% van de nieuw opgespoorde patiënten WHO grade 2 zal hebben. Onder deze aanname voorspellen wij dat in het 'worst case' scenario 830.000 nieuwe patiënten zullen worden opgespoord met WHO grade 2 gedurende 2001-2020. De voorspelde aantallen voor het doorsnee en het 'best case' scenario zijn respectievelijk 500.000 en 300.000.

De prevalentie van personen met gebreken volgt door te berekenen hoe lang al bestaande en nieuwe patiënten met WHO grade 2 zullen blijven leven. Leeftijdsspecifieke sterftekansen zijn toegepast en er is geen oversterfte aangenomen omdat lepra in principe niet dodelijk is. Volgens de literatuur bedraagt het aantal opgespoorde nieuwe patiënten met WHO grade 2 tussen 1985-1998 680.000. Schattingen voor de jaren voor 1985 zijn verkregen via extrapolatie terug in de tijd. Volgens de overlevingsberekeningen bedroeg de wereldwijde prevalentie van personen met WHO grade 2 aan het eind van 2000 1,3 miljoen. De voorspelde wereldwijde prevalentie in het jaar 2020 is 1,4 miljoen in het 'worst case' scenario, 1,1 miljoen in het doorsnee scenario en 0,9 miljoen in het 'best case' scenario. Deze resultaten geven aan dat de vereiste zorg voor personen met gebreken in het beste geval slechts langzaam zal verminderen.

De conclusies en aanbevelingen die volgen uit het onderzoek voor dit proefschrift zijn geformuleerd in de Discussie (**Hoofdstuk 9**), en worden hieronder samengevat.

Conclusies

- Er is tot nu toe geen algemene afname in de jaarlijkse aantallen opgespoorde leprapatiënten in de belangrijkste endemische landen.
- De invloed van chemotherapie en BCG vaccinatie op de transmissie en incidentie van lepra is hoogst onzeker.
- Deze onzekerheid wordt grotendeels veroorzaakt door drie openstaande vragen over besmettelijkheid en transmissie:

- vindt de transmissie van lepra voornamelijk plaats naar nauwe contacten van besmettelijke individuen of naar de bevolking in het algemeen?
- in welk tempo besmetten besmettelijke individuen vatbare individuen?
- in welke mate dragen individuen zonder symptomen van lepra bij aan transmissie?

- De prevalentie van zenuwbeschadigingen en lichamelijke gebreken onder nieuw gediagnostiseerde leprapatiënten neemt sterk toe met een langere duur van opsporing.

- Het reeds aanwezig zijn en de ernst van zenuwbeschadigingen en lichamelijke gebreken bij diagnose van een leprapatiënt is de belangrijkste determinant voor het hebben van gebreken op een later tijdstip.

- Het aantal individuen in de wereld met zenuwbeschadigingen en lichamelijke gebreken ten gevolge van lepra zal in de nabije toekomst in het beste geval slechts zeer langzaam afnemen.

Aanbevelingen

- Het peil van de huidige leprabestrijding op basis van chemotherapie moet nog minstens tien jaar worden vastgehouden. Daarna moeten lepratrends opnieuw worden geanalyseerd om te beoordelen of de bestrijding minder intensief kan worden.

- Bestrijdingsprogramma's moeten nadruk leggen op de verkorting van de opsporings-duur omdat vroege opsporing essentieel is voor de preventie van zenuw-beschadigingen en lichamelijke gebreken èn voor de preventie van transmissie.

- Een strategie waarbij verschillende disciplines van lepraonderzoek worden gecombi-neerd is noodzakelijk om de openstaande vragen over besmettelijkheid en transmissie te onderzoeken.

- Voor simulatiemodellering is een rol weggelegd in het gedetailleerd onderzoeken van transmissiepatronen van lepra in populaties, en in de bestudering van de potentiële invloed van primaire preventie gericht op nabije contacten van leprapatiënten.

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Curriculum vitae

Abraham Meima was born on August 20, 1963 in Vlissingen (The Netherlands). In 1981, he passed his secondary school exam at the Rijksscholengemeenschap Scheldemond in Vlissingen and started studying Mathematics at the University of Leiden. He specialised in 'Applied Mathematics' and graduated in 1987. From 1987 to 1990, he took the technological designer course 'Management Engineering' at the Delft University of Technology. He completed this training in a collaborative project with the European Space & Technology Centre ESTEC in Noordwijk. He worked as consultant for the Informatics Center for Infrastructure and Environment in Rijswijk from 1990 tot 1993.

In July 1993, he joined the Department of Public Health, Erasmus MC, University Medical Center Rotterdam. He investigated the impact of leprosy control on the occurrence of leprosy and health problems caused by leprosy. Epidemiological/ mathematical modelling played an important role in his research. Collaborative projects were undertaken with the CJIL Field Unit (Indian Council of Medical Research); All African Leprosy, Tuberculosis and Rehabilitation Training Centre, Ethiopia; University of Bergen, Norway; McKean Rehabilitation Center, Thailand; University of Aberdeen, Scotland; Danish-Bangladesh Leprosy Mission, Bangladesh. Collaboration with the last two partners continues in ongoing projects. He is coordinator of the annual two-week course 'Quantitative Models for Evaluation of Tropical Disease Control'. His present research activities also cover tuberculosis.

Curriculum vitae

Abraham Meima werd geboren op 20 augustus 1963 te Vlissingen. Hij haalde daar in 1981 het atheneum diploma aan de Rijksscholengemeenschap Scheldemond. Tussen 1981 en 1987 studeerde hij Wiskunde aan de Rijksuniversiteit Leiden. Zijn afstudeerrichting was 'Toegepaste Wiskunde'. In 1987 startte hij de vervolgopleiding 'Wiskundige Beheers- en Beleidsmodellen' aan de Technische Universiteit Delft. Deze opleiding rondde hij af in 1990 via een project dat werd uitgevoerd in samenwerking met het ruimtevaart-laboratorium ESTEC te Noordwijk. Tussen 1990 en 1993 was hij werkzaam bij het Informaticacentrum voor Infrastructuur en Milieu (Icim).

Sinds juli 1993 is hij in dienst bij de afdeling Maatschappelijke Gezondheidszorg van het Erasmus MC, Universitair Medisch Centrum Rotterdam. Hij onderzocht de invloed van leprabestrijding op het vóórkomen van lepra en op de ernst van gezondheidsproblemen ten gevolge van lepra. Epidemiologische/wiskundige modellering speelde een belangrijke rol in het onderzoek. In projecten werd samengewerkt met de CJIL Field Unit (Indian Council of Medical Research); All African Leprosy, Tuberculosis and Rehabilitation Training Centre, Ethiopië; Universiteit van Bergen, Noorwegen; McKean Rehabilitation Center, Thailand; Universiteit van Aberdeen, Schotland; Danish-Bangladesh Leprosy Mission, Bangladesh. De laatste twee partners zijn ook nauw betrokken bij huidige studies. Zijn onderzoeksterrein heeft zich inmiddels uitgebreid naar tuberculose. Voorts is hij coördinator van de jaarlijkse tweewekelijkse cursus 'Quantitative Models for Evaluation of Tropical Disease Control'.

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