

# ***Mycobacterium leprae* and reasons for decline in the global prevalence of leprosy since the 1970s**

by  
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## Abstract

Leprosy is a communicable infectious disease caused by *Mycobacterium leprae*. Many patients have been infected with *M. leprae* throughout the years, and until recently the disease was difficult to treat. In the past, lack of efficient drugs resulted in a high cumulative number of leprosy patients. According to the World Health Organization (WHO) the global registered prevalence has fallen dramatically during the last 30 years, and we wanted to look into the reasons for this decline.

Methods: Searches performed using PubMed and WHO's websites and library databases.

Results: Several events can explain the decline in prevalence: inactivation of cases and release from control, introduction of multidrug therapy (MDT), reduction in treatment length, time of year for the registration of prevalence and alterations of definitions.

Conclusions: A consequence of these operational changes has been a fall in prevalence from an estimated 11 million in 1970 to 0.2 million registered cases in 2008. However, leprosy is still a global challenge. Even though estimated prevalence has decreased dramatically from the 1980s, new cases detected (NCD) have remained rather static over the same period of time.

## Abbreviations and explanations

APC	Antigene-presenting cell
BB	Borderline leprosy
BCG	Bacille Calmette Guérin
BI	Bacterial index
BL	Borderline lepromatous leprosy
BT	Borderline tuberculoid leprosy
ENL	Erythema nodosum leprosum
FSH	Follicle-stimulating hormone
HLA	Human leucocyte antigene
I leprosy	Indeterminate leprosy
Ig	Immunoglobulin
IL	Interleucin
INF	Interferon
LH	Luteinizing hormone
LL	Polar lepromatous leprosy
<i>M. avium</i>	<i>Mycobacterium avium</i>
MB	Multibacillary
<i>M. bovis</i>	<i>Mycobacterium bovis</i>
MDT	Multidrug therapy
MHC	Major histocompatibility complex
<i>M. leprae</i>	<i>Mycobacterium leprae</i>
<i>M. tuberculosis</i>	<i>Mycobacterium tuberculosis</i>
NCD	New case detected
NCDR	New case detection rate
PB	Paucibacillary
PCR	Polymerase chain reaction
PGL	Phenolic glycolipid
SSL	Single skin lesion
Th	T-helper cell
TNF	Tumor necrosis factor
TT	Polar tuberculoid leprosy
UVR	Ultraviolet radiation

Incidence: The number of new cases of a disease within a specified time period.

Incident case: New case, with or without obvious symptoms and signs of leprosy, prior to diagnosis and start of treatment

Incidence rate: The number of new cases of a disease within a specified time period divided with the total population.

NCD: The number of new leprosy cases that are registered as patients in a given period.

NCDR: The number of new leprosy cases that are registered as patients in a given period divided with the total population

Prevalence: The total number of cases of a disease in a population at a given time. In this text per 31st of December each year.

Prevalence rate: All patients receiving treatment at a defined point of time divided with the total population.

## **1 Introduction**

### **1.1 Purpose**

Leprosy has for centuries been a dreaded disease for which there until recently was no cure.

Since the 1970s the number of cases world wide has fallen from an estimated 10.8 million (1) to a registered prevalence of 212802 (2) at the beginning of 2008. We wanted to investigate the causes of this extreme decline and our approach became “reasons for decline in global prevalence of leprosy since the 1970s”. To be able to answer this question it was necessary for us to learn as much as possible about the disease.

### **1.2 Methodology**

We have mainly been searching in PubMed for articles on leprosy published after 1990. We used the search terms “leprosy”, “epidemiology”, “genomic”, “pathogenesis”, “MDT”, “*Mycobacterium leprae*”, “transmission”, “number” and “incidence”. Only papers published in English were considered. We also used the WHO website and WHO Library database to find publications and documents concerning leprosy published between 1970 and today.

## **2 Background on leprosy**

### **2.1 Introduction**

Leprosy has been known since ancient times. The first known written text about leprosy is dated 600 BC. (3) It is a communicable disease caused by *Mycobacterium leprae* (*M. leprae*). The disease is also called Armauer Hansens disease (4), since the bacteria was discovered by G. A Hansen in 1873 (5). When it was discovered, *M. leprae* was the first bacteria identified as a cause of human disease (5).

### **2.2 Aetiology**

Leprosy is a granulomatous infectious disease. The bacillus is an obligate intracellular (6) acid-fast staining rod, 1-8 µm long and 0.3 µm in diameter (7), which grows best at 27-30 °C. This corresponds with the temperature in the main target organs like dermis, peripheral nerves, nasal mucosa, upper respiratory tract and eye. (6)

The doubling time varies from 11-12 days to 20-30 days in different literature (7, 8) and the incubation period may vary from months to 30 years. On average the incubation period is 4 years in tuberculoid

leprosy and 10 years in lepromatous leprosy. (9)

The genome includes 1605 protein coding genes and 50 stable RNA-molecule coding genes. It looks as though *M. leprae* has a lack of some regulatory and metabolic genes which means that it has lost its ability for replication ex vivo and because of that needs to grow inside host cells. This can explain the long generation time. (9) *M. leprae* cannot be cultured on artificial media, (10) which previously inhibited studies in vitro. The organism can replicate in the mouse footpad and the nine-banded armadillo which have provided bacteria for study. (9)

### **2.3 Classification**

Ridley and Jopling created a classification system of leprosy in 1966. This classification is based on the immunologic response of the host to *M. leprae*, and divides patients into a five group system:

- 1 Polar tuberculoid leprosy (TT)
- 2 Borderline tuberculoid leprosy (BT)
- 3 Borderline leprosy (BB)
- 4 Borderline lepromatous leprosy (BL)
- 5 Polar lepromatous leprosy (LL)

(4, 11)

In addition there are a group called indeterminate (I) leprosy. This is a form that if left untreated, may progress to tuberculoid, borderline or lepromatous disease. (12)

In 1982 the World Health Organization (WHO) study group on Chemotherapy of Leprosy for Control Programmes (13) classified leprosy patients into multibacillary (MB) or paucibacillary (PB). MB leprosy included LL, BL and BB. PB leprosy included I, TT and BT with bacterial index (BI) < 2.

In 1988 WHO decided that PB leprosy should include only smear-negative (BI=0) I, TT and BT. Any patient in these groups with smear-positivity (BI ≥ 1) was classified as MB. MB leprosy then included BB, BL and LL as well as every other with smear-positivity. (14, 15, 16) This recommendation was an attempt to avoid further treatment failure of PB patients with positive skin smear. (11) When classification was in doubt, the patient was to be treated as having MB leprosy. (17)

Services for processing skin smears were not available all over, and even if it were available the reliability was often doubtful. In addition, one assumed that the protective immunity was inversely correlated with the number of lesions so that MB patients had a greater number of lesions. As a consequence, in 1998 WHO (18) declared that patients could be classified into three groups on the basis on skin lesions:

Single skin lesion (SSL): one skin patch.

Paucibacillary: 2-5 skin patches.

Multibacillary: > 5 skin patches.

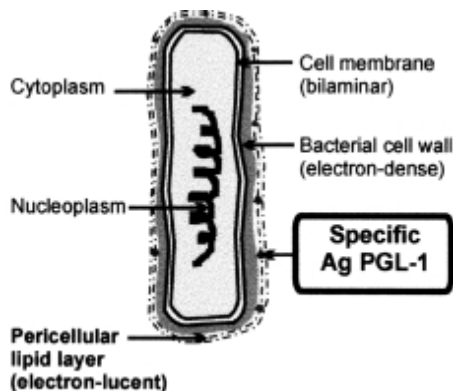
	<b>SSL</b>	<b>MB</b>	<b>PB</b>
<b>Skin patch</b>	<b>1</b>	<b>&gt;5</b>	<b>2-5</b>
<b>Skin smear</b>		<b>+</b>	<b>-</b>
<b>Sub groups</b>		<b>BB, BL, LL</b>	<b>TT, BT</b>

**Figure 1:** Today leprosy may be classified determined by the number of skin patches and/or number of bacilli in skin smear.

## 2.4 Pathogenesis

### 2.4.1 The structure of *M. leprae*

*M. leprae* belongs to the *Mycobacteriaceae* family and the genus *Mycobacterium* (19). Almost 100 species of mycobacteria have been identified, and many are associated with human disease. *M. leprae* is weakly gram-positive and a strongly acid-fast rod. (10) It does not release any toxins (8). The bacterium consists of a spiralled nucleoplasm surrounded by a dense homogeneous cytoplasm, lined by a plasma membrane and a thick bacterial cell wall. *M. leprae* shares several antigens with *M. tuberculosis*. Specific antigenic structures have been detected in the outer layer of *M. leprae*, mostly phenolic glycolipid I (PGL-I) (8). PGL-I is an important target for the host immune response, by stimulating IgM antibody response. (9)



**Figure 2:** The basic structure of *M. leprae* (8)

### 2.4.2 *M. leprae* and its targets

*M. leprae* enters the lymph and blood vessels to reach its targets. There are three main targets (8):

- 1 Schwann cells.
- 2 Monocyte-macrophage system.
- 3 Endothelial cells and pericytes.

#### 2.4.2.1 The Schwann cell

The unique predilection of *M. leprae* for Schwann cells is probably determined by the mycobacterium's binding to laminin-2, which is a component of the basal lamina of Schwann cells (9). It is the globular (G) domain of the  $\alpha 2$  chain of laminin-2 that is the specific subunit with which *M. leprae* interacts (20). This form of laminin is restricted to peripheral nerves which explain the specific tropism of *M. leprae* (9). Laminin-2 is anchored to Schwann cells via the laminin receptor which have been shown to be the  $\alpha$ -Dystroglycan receptor (20). The uptake of *M. leprae* by the Schwann cell depends on the laminin- $\alpha$ -Dystroglycan-complex in the cell membrane of the Schwann cell. Several molecules on the surface of *M. leprae* binds to this complex, including PGL-1 and the bacterial adhesion LBP21/Hlp, which potentiates the interaction of *M. leprae* with the Schwann cell. (9, 20)

The binding of *M. leprae* to the Schwann cell leads to phagocytosis of the bacteria. Normally, phagosomes undergo a series of events that ends when the phagosome fuse with lysosomes and the content of the phagolysosome is then degraded. It seems that phagosomes containing other pathogenic mycobacteria, including *M. tuberculosis*, *M. bovis* and *M. avium*, are arrested for phagosomal development in an early state. This enables these mycobacterial species to survive the normally hostile intracellular environment by avoiding fusion with the lysosome. Studies suggest that trafficking of *M. leprae* through the Schwann cell endocytic pathway may be similar to other mycobacteria studied.

Similar results have been obtained in macrophage cell line. This indicates an active process by which these organisms perpetuate in the host cell. (20) Inside the phagosomes the bacilli are protected from antibodies and macrophages, and they may survive for years and replicate slowly (8, 9).

The Schwann cell can express HLA class 2 molecules and presents mycobacterial peptides on its surface. At some stage, CD4+ T-cells recognize the presence of mycobacterial antigens within the nerve and initiate a chronic inflammatory reaction. The perineurium around the nerves is inflexible and swelling of the nerves will therefore lead to ischemia, further nerve damage and eventually fibrosis with axonal death. (9)

#### 2.4.2.2 The monocyte-macrophage system

All cell-mediated and humoral immune responses require starting cells. Antigen presenting cells (APC) express the antigenic information on their surface and, in concert with MHC, initiate the immune cascade. Different cells can act as APCs. Macrophages may act as such starting cells, or APC, and are therefore of utmost importance concerning leprosy (8). Different clones of macrophages may evolve into different APCs, and are associated with cell-mediated or humoral immunity (8).

When *M. leprae* leaves the Schwann cells and penetrate the perineural tissues they meet macrophages as histiocytes. (8) The macrophages engulf the bacilli within phagosomes, where the bacilli may replicate. Simultaneously, the activated macrophages produce lysosomes filled with hydrolytic enzymes. These lysosomes tend to fuse with phagosomes to form a phagolysosome. (8, 20)

There are two types of macrophages among leprosy patients. Among patients with TT or BT, the macrophages may destroy all bacilli and obtain normal antigenic information. Macrophages may then act as APC to stimulate cell-mediated immunity. The activated macrophages express MHC class II and produce IL-12. IL-12 stimulates CD4+ T lymphocytes to produce IL 2 and INF- $\gamma$ . New macrophages may then be activated and transformed into epithelioid cells. (8)

Among patients with LL or BL on the other hand, the macrophages have a functional deficiency of lysosomal phospholipases. So when the lysosomal enzymes reach the bacilli only partial lysis occur. (8) Because the lysis is only partial, antigenic information is incomplete and the cells cannot act as APC. The macrophages will develop into lepra cells with persistent bacterial phospholipids. When these cells age they may be engulfed by other macrophages, that act as APC, and stimulate humoral immunity. (8)

Because of the different response of the macrophages to *M. leprae* two types of granulomas develop. Epithelioid granulomas are seen in tuberculoid leprosy. They consist of epithelioid cells, which are stimulated histiocytes differentiated into macrophages, and scarce or no bacilli. Lepromatous granulomas, which contain lepra cells, dominate in lepromatous leprosy. Lepra cells are macrophages with an abundant cytoplasm filled with irregular microvacuoles. Within these vacuoles, PGL-1 may be identified. In borderline leprosy, both types of granulomas may coexist. (8)

#### 2.4.2.3 Endothelial cells

*M. leprae* has been found in endothelial cells lining the blood vessels and the lymphatics. This suggests that endothelial cells in the epineurial and perineurial blood vessels may be a reservoir for actively replicating *M. leprae*. The bacteria can then infect the Schwann cells in adjacent tissue or reach the peripheral nerve tissue through the bloodstream. (20) Through the cytoplasm of the endothelial cells, *M. leprae* may migrate to the perivascular connective tissue and be ingested by macrophages. (8)



### 2.4.3 Genetics of host susceptibility

Leprosy has different clinico-pathologic forms, tuberculoid and lepromatous leprosy, determined by the underlying immunological response to *M. leprae*. Studies of human leukocyte antigens (HLA) and proteins encoded by MHC-linked genes, have revealed the predominance of MHC class II: HLA-DR2 and HLA-DR3 in tuberculoid leprosy and HLA-DQ1 in lepromatous leprosy. (8, 9)

Patients with tuberculoid leprosy have a vigorous cellular immune response to *M. leprae*, which limits the disease to a few well-defined skin patches or nerve trunks. The lesions are infiltrated by INF- $\gamma$  secreting CD4+ T-cells which form well-demarcated granulomas, containing epithelioid and multinucleate giant cells. These are located around dermal nerves. Few, if any acid-fast mycobacteria are found in the lesions. Skin and nerve lesions are infiltrated by Th1-like T-cells which produce INF- $\gamma$ , TNF- $\alpha$  and IL - 2 and 15. Antibody responses to *M. leprae* antigens are absent or weak. (9)

Lepromatous leprosy is characterised by the absence of specific cellular immunity. There is therefore uncontrolled proliferation of leprosy bacilli with many lesions and extensive infiltration of the skin and nerves. The dermis contains foamy macrophages filled with many bacteria but few CD4+ and CD8+ T-cells and no organised granulomas. There are high titres of antibodies to PGL-1 and protein antigens specific for *M. leprae*. Lesions contain mRNA for IL-4 and 10 which are produced by Th2-like cells. (9)

Most patients have one of the intermediate forms of leprosy: BT, BB or BL. These forms are characterised by a progressive reduction from BT to BL leprosy in cellular responses, associated with an increasing bacillary load, more frequent skin and nerve lesions and higher antibody titres. The borderline forms are clinically unstable, and patients either show change towards the lepromatous pole or experience a sudden type 1 reaction. (9)

## 2.5 Transmission

### 2.5.1 Transmission among individuals

Leprosy is, contrary to what many believe, not a very infectious disease. It requires long and frequent contact with untreated cases to get infected because >99% of the population has adequate natural immunity, >85% of the clinical cases are non-infectious and an infectious patient become non-infectious by the end of the first week of treatment. (21)

It is not fully understood how *M. leprae* is spreading from one individual to another. However, it has been shown that the bacteria cannot penetrate intact skin and the infection is not spread by touching. Probably, the bacteria spread by aerosols from nasal secretions and are then taken up by nasal or respiratory mucosa. (9) Entry of *M. leprae* through broken skin cannot be ruled out, although it is most likely that the main entry is through the respiratory tract. Rees and McDougall did in 1977 succeed in the experimental transmission of leprosy through aerosols containing *M. leprae* in immune-suppressed mice. This suggests a similar possibility in humans. Successful results have also been reported in experiments with mice when *M. leprae* was introduced to the nasal cavities through topical application. (22) The bacillium has been found in nose secret from patients with lepromatous leprosy (9) and an ulcerated nasal mucosa from a patient with multibacillary leprosy can yield over 10 million viable bacilli every day. (6)

*M. leprae* DNA has been found in nose secret in up to 5% of healthy individuals in India and Indonesia which suggest that subclinical infection occurs, (9) and that healthy individuals may be a source of infection. Scientists are not certain when, throughout the period of incubation and clinical disease, an individual is particularly infectious. Saunderson writes in a paper from 2008 (23) that incident cases are

the ones actively transmitting the disease to others whom they have had social or household contact with.

In a paper written by Mastrangelo G et al. (24) there are summarised several studies on nasal carriage.

- When Hatta et al. examined 418 individuals repeatedly over a period of 2 years they found that 2.9% were PCR positive for *M. leprae*. But the PCR-positivity was not persistent over the 2 years. This indicates that nasal carriage is transient.
- Beyene et al. found that in a village in Ethiopia 5.9% of the individuals without clinical signs of leprosy were positive for *M. leprae* DNA.
- Smith et al. examined and followed up over 2 years 2252 people living in 3 leprosy endemic countries. Nasal swabs and saliva collections were tested, and 1.6% of nasal swabs were PCR positive against 68% of saliva samples positive for *M. leprae* IgA. PCR-positivity did not persist.
- Job et al. evaluated the presence of *M. leprae* in the unbroken skin and nasal secretions of MB leprosy patients and their contacts. 80% of untreated MB patients had acid-fast bacilli in the keratin layer when examined histologically. By PCR studies it was found that 80% of the patients had *M. leprae* DNA in skin washings and 60% had *M. leprae* DNA on swabs obtained from nasal mucosa. When contacts of untreated MB cases were tested PCR analysis showed that 17% had skin positivity and 4 % nasal positivity. 2 months after treating the index case all contacts tested were negative for *M. leprae* DNA. These data suggested that both skin and nasal epithelium of untreated MB leprosy patients contribute to the shedding of *M. leprae* into the environment and that people that are in contact with untreated MB cases are at risk for contact with *M. leprae* through both the nasal mucosa and exposed surfaces of their skin.

Although nasal carriage does not necessarily imply infection or excretion of bacilli, the finding of nasal carriage supports the theory of a disseminated occurrence of *M. leprae* in populations for which leprosy is endemic. (24)

### 2.5.2 Survival of *M. leprae* outside the human body

Under tropical conditions the bacteria may survive for up to 9 days outside humans. (6) Davy and Rees reported in 1977 that *M. leprae* from nasal secretion could survive 36 hours or more outside humans under normal conditions. (22) Survival of *M. leprae* outside the human body has also been detected in several other studies referred to in a paper written by Mastrangelo G et al. in 2008 (24):

- Desikan and Sreevatsa did in 1995 verify the viability outside the human body of *M. leprae* obtained from untreated patients: 60 days in saline at room temperature, 36 days in wet soil and 7 days on exposure to direct sunlight for 3 hours a day.
- Kaur et al. checked the viability of *M. leprae* harvested from fresh lepromas and injected into the footpads of thymectomized mice. They found that the bacteria were able to survive 7 days at room temperature, 2 hours of exposure to direct sunlight and 30 min of exposure to UVR.

These findings increase the possibility of spread of infection through broken skin (6) and suggest the possibility that contaminated clothing and other fomites may act as sources of infection. (22)

*M. leprae* DNA has also been detected by PCR from 21 out of 44 water sources used daily by villagers. Prevalence of leprosy among people using PCR-positive water for bathing and washing was significantly higher than among people who used PCR-negative water. No significant difference in prevalence was recognized in case of usages of negative or positive water for drinking. (24)

It is not possible to exclude insects as a source of infection. (22) Natural infection in primates such as the armadillos, chimpanzees and mangabey monkeys has been reported, but the significance of these findings is unknown. (18)

## **2.6 Clinical features**

Leprosy affects many organs, for instance skin, nerves, eyes and some internal organs. (9, 25) The clinical features depend on the hosts' immunologic response to *M. leprae*. (11) The disease progresses slowly, especially in early phases. (4) Patients commonly present with skin lesions or weakness and numbness caused by peripheral nerve lesions. Peripheral nerve damage may also cause more severe paresthesia and paresis, and burns or ulcers in anaesthetic hands/feets can develop. If the disease is allowed to progress, systemic features may develop. (9) Untreated leprosy cause progressive and permanent damage. (4) If detected early and treated with MDT however, leprosy will not lead to disabilities. (26)

Leprosy can affect all ages and both sexes. (26) The peak age of onset is young adulthood, usually 20-30 years of age. The disease is rarely seen in children less than five years old. (27) Although leprosy affects both sexes, in most parts of the world males are affected more frequently than females, often in the ratio of 2:1. This male predominance is however not universal, and there are several areas where there is either equal occurrence of leprosy in the two sexes, or occasionally even a higher prevalence among females. (22)

### **2.6.1 Skin**

The skin is involved in almost all patients. (25) The most common skin lesions are macules or plaques. More rarely papules and nodules are seen. (9) The patches can be reddish, pale or copper-coloured, and the patches lack sensation to heat, touch and pain. Diffuse thickening of the skin without loss of sensation may also be a sign of leprosy. The skin lesions may appear anywhere on the body. They usually do not hurt, and do not itch. (26)

**Tuberculoid leprosy:** Typically few, well-defined, asymmetric plaques with dry, scaly skin. The lesions are hypo-pigmented and hairless, and most often infiltrated with a raised edge. On pale skin, lesions can appear erythematous. The sensitivity of the skin patches is usually diminished. (4, 9)

**Lepromatous leprosy:** Patients with lepromatous leprosy have many lesions, most often macules. The macules are symmetrically distributed on the body, and may confluent in some cases and give diffuse thickening of the skin. The macules have a smooth and shiny surface. The lesions are not well-defined from normal skin. Loss of body-hair is normal, especially eyebrows. As opposed to tuberculoid leprosy, many of the skin lesions are not hypoaesthetic. (4, 9)

**Borderline leprosy:** Skin lesions compatible with both tuberculoid and lepromatous leprosy are seen. The skin patches may therefore differ in their appearance.



**Figure 3:** Skin lesions in a patient. (26)

### **2.6.2 Nerves**

Both peripheral nerves and small dermal nerves are affected. The posterior tibial nerve is most commonly affected, followed by the ulnar, median and lateral popliteal nerve and facial nerves. (9) Most nerves are affected bilaterally, but unilateral involvement may be seen in tuberculoid cases. (25) Involvement of the nerves produces enlargement, with or without tenderness, and standard regional

patterns of sensory and motor loss. Autonomic nerves may also be affected, and cause anhidrosis, iris dysfunction, cardiac rhythm disturbances, decreased response to cough and neurogenic bladder. (9, 25) As a general rule, the brain, meninges, cerebellum and spinal cord are not directly infiltrated by *M. leprae*. However, spinal cord degeneration and abnormalities of the brainstem due to peripheral neuritis have been observed. (25)

Pure neuritic leprosy is seen in India and Nepal, where it accounts for 5 – 10 % of the leprosy patients. Clinically, these patients present with asymmetrical involvement of peripheral nerve trunks and no visible skin lesions. Histology of a nerve biopsy sample might reveal any type of leprosy. (9)

Tuberculoid leprosy: There are typically enlarged single nerve, with early nerve damage that causes e.g. drop-foot or claw-hand (4). Sensory nerves are also affected, producing hypoaesthesia.

Lepromatous leprosy: Nerve damage appears late, but progresses. Glove and stocking sensory loss is common in lepromatous disease. (4)

### 2.6.3 Systemic features

Systemic features are mainly seen in lepromatous patients as a result of bacillary infiltration. (9)

#### Eyes

Eye damage results from both nerve damage and direct bacillary invasion. (9) The most common ocular involvement occurs in the periorbital tissues and in the anterior half of the eye, including the ciliary body, iris, choroid, sclera and cornea. The posterior half of the eye and the optic nerve is usually spared. (25) Lagophthalmus results from paresis of the orbicularis oculi muscle caused by involvement of the zygomatic and temporal branches of the facial (VIIth) nerve. Damage to the ophthalmic branch of the trigeminal (Vth) nerve causes anaesthesia of the cornea and conjunctiva, which results in dry, insensitive corneae and reduction in blinking. These effects leave the cornea at risk of minor trauma and ulceration. (9) Other conditions that may be present are iridocyclitis, conjunctivitis, keratitis, cataracts, uveitis and glaucoma, which all can contribute to decreased vision. (25) The worst outcome of eye involvement is blindness.

#### Respiratory system

*M. leprae* mostly affects the upper portions of the respiratory tract. Nasal septum perforation with collapse, laryngeal and tracheal involvement are common, especially in MB patients. The epiglottis is almost always involved. Common symptoms are cough, hoarseness and occasionally breathlessness. The larger bronchi are affected at a lesser extent, while the lung parenchyma is usually spared. (25)

#### Liver

Involvement of the liver is seen in both MB and PB patients, but in larger amount among MB patients. Leprosy reactions can worsen underlying liver diseases, but do not seem to be a primary cause of hepatitis. On the other hand, there has been reports of increased risk for viral hepatitis in leprosy patients. The most common liver involvement is presence of granulomas in the liver parenchyma. The granulomas are a direct result of the haematogenous spread of *M. leprae*, and may be related to the duration of the disease and the number of circulating organisms in the blood. Hepatic involvement is usually asymptomatic with normal liver function tests. Secondary amyloidosis of the liver is also seen, mostly in lepromatous patients. This can result in hepatomegaly. (25)

#### Male reproductive system:

Elevated serum levels of FSH and LH and decreased testosterone levels are common. This may contribute to common complaints of impotence, sterility and decreased libido. (25) Loss of testosterone is caused by orchitis and testicular atrophy and leads to azoospermia, gynaecomastia and impotence. (9)

## **2.7 Disabilities as a consequence of leprosy**

### **Grading of disabilities:**

#### 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.

Damage includes ulceration, shortening, disorganization, stiffness and loss of part or all of the hand and feet.

#### Eyes

Grade 0: No eye problems due to leprosy; no evidence of visual loss.

Grade 1: Eye problem due to leprosy present, but vision not severely affected (vision 6/60 or better; can count fingers at six meters).

Grade 2: Severe visual impairment (vision worse than 6/60; inability to count fingers at six meters), corneal opacities, lagophthalmus or iridocyclitis.

(15, 28)

## **2.8 Leprosy reactions**

The dynamic nature of the immune response to *M. leprae* leads to spontaneous fluctuations in the clinical condition. This is called leprosy reactions. (9) Up to 30% of MB-patients have acute inflammatory episodes involving skin and nerves. (29)

Leprosy reaction is an acute inflammatory response and is a natural course for the disease. It is not a side effect of MDT and does not mean that the treatment is not working.

Existing skin-lesions becomes reddish and swollen, and painful reddish nodules appear. The peripheral nerves are painful, swollen and tender. Loss of sensibility and muscle weakness are signs of nerve damage. The patient may develop fever and malaise, and hands and feet may become swollen. (26)

Triggering factors include physical and mental stress, multidrug therapy (MDT), vaccination, pregnancy, surgery, infection and other antibacterial treatment. (11)

### **2.8.1 Type 1 reaction**

Type 1 reaction occurs in 1/3 of patients with borderline forms (9) and possibly also in TT. This is a cellular mediated allergic reaction (11) and is caused by a spontaneous increase in T-cell reactivity to mycobacterial antigens. There is infiltration of INF- $\gamma$  and TNF- $\alpha$  secreting CD4+ lymphocytes in the skin and nerves. This results in oedema and painful inflammation. During the reaction the peripheral blood lymphocytes increase their cytokine production and as a result serum cytokine concentration also increases. The levels fall under treatment with corticosteroid, but patients with high cytokine levels respond poorly to the treatment and they are more likely to relapse after the corticosteroid treatment (9) This emphasises the importance of rapid suspicion of leprosy reaction and treatment to prevent further nerve damage.

### **2.8.2 Type 2 reaction**

Type 2 reaction, or erythema nodosum leprosum (ENL), is a systemic inflammatory response to the deposition of extravascular immune complexes leading to infiltration of neutrophils and activation of complement in many organs. (9) This is a humoral reaction (11) that only occurs in BL and LL. There are high concentrations of circulating TNF- $\alpha$ . (9) Erythematous nodules and widespread painful swelling of peripheral nerves develop. (11)

### 2.8.3 Type 3 reaction

A third type of reaction is called the “Lucio Phenomenon”. This is rare and is only seen in a subtype of LL called primary diffuse lepromatous leprosy. It is most common in Central and South America. The reaction is characterised by a diffuse granulomatous infiltration in the skin with a high bacterial number. (11)

### 2.8.4 Treatment of leprosy reactions

A patient that gets symptoms and signs of leprosy reaction must be treated immediately. Without treatment irreversible deformities may develop. The treatment is aspirin or paracetamol to reduce the pain and fever, plus corticosteroids in dosages (26):

40 mg daily for weeks 1 and 2

30 mg daily for weeks 3 and 4

20 mg daily for weeks 5 and 6

15 mg daily for weeks 7 and 8

10 mg daily for weeks 9 and 10

5 mg daily for week 11 and 12

Prednisolone suppresses reactions and ameliorates acute nerve damage in about 60% of patients. (29) It is important that the patient continues with MDT during the leprosy reaction. (26)

## **2.9 Diagnosis**

The diagnosis of leprosy is clinical, and based on the patient’s symptoms and clinical signs. Only in rare instances is there a need to use laboratory and other investigations to confirm the diagnosis of leprosy. (16) The diagnosis is simple but it requires skill to differentiate skin-lesions and recognize nerve involvement. (30) In the pre-MDT era, the great majority of leprosy cases were diagnosed by medical officers or specialized leprosy workers. Because not all patients had access to such specialized workers, diagnosis and treatment was often delayed. Since the introduction of MDT, many procedures have been simplified and general health workers have been trained so that as many patients as possible can be diagnosed in the field. (18)

### 2.9.1 Diagnostic criteria

WHO recommends (16) that: In an endemic country or area, an individual should be regarded as having leprosy if he or she shows ONE of the following cardinal signs:

- 1) Skin lesion consistent with leprosy and with definite sensory loss, with or without thickened nerves.
- 2) Positive skin smears.

The quality of skin smears still remains poor in a majority of programmes, even though resources have been spent trying to upgrade it. Because classifying leprosy is possible without skin smear result, the skin smear service may only be utilized if it already exists and functions adequately. Skin smear services should not be a prerequisite for implementing MDT. (18)

### 2.9.2 Clinical examination

During the clinical examination it is important to inspect the whole body in daylight or in a well-lit room. Skin lesions should be examined for hypoaesthesia to light touch, pin-prick and temperature. The skin should also be examined for anhidrosis. (9) After examining the skin, all superficial peripheral nerves should be palpated. The nerves should be examined for tenderness, size, enlargement and consistency. Subsequently, sensory and motor functions should be tested. (31) Autonomic nerve function is tested by examination of skin temperature, skin colour, dryness and hair amount.

### 2.9.3 Supplementary tests

#### Skin smear

Fite's method (4) is used to investigate infected skin for rod-shaped and red-stained acid-fast bacilli (16). Small incisions are made on the skin, using a sharp scalpel. Interstitial extracellular fluid from the cut is spread fairly thickly on a slide. The material is then stained using modified Ziehl Nielsen's method and decolorized (but not completely) with 1 % acid alcohol. (32)

The skin smears are examined under a 100x oil immersion lens. Six to eight stained smears are counted for bacteria, and used to calculate the bacterial index (BI). This is an expression of the extent of bacterial loads (number of bacillus pr field). The results are expressed on a logarithmic scale.

BI	Bacterial load
0	0 per 100 fields
1+	$\geq 1$ per 100 fields
2+	$\geq 1$ per 10 fields
3+	$\geq 1$ per field
4+	$\geq 10$ per field
5+	$\geq 100$ per field
6+	$\geq 1000$ per field

**Figure 4:** Bacteriological index (BI) dependent on bacteria in field (32).

Positive skin-smear:  $BI \geq 1$

Negative skin-smear:  $BI = 0$

(14, 16)

The BI is valuable because it is simple and is representative of many lesions, but it is affected by the depth of the skin incision, the thickness of the film, the staining and the interpretation of the slide. (11, 32)

Skin smears have high specificity, but low sensitivity. This is because 70 % of all leprosy patients are smear negative. (9) However, there is no need to take skin smears for diagnosis because leprosy can be easily diagnosed and classified on the basis of clinical findings. Unnecessary skin-piercing procedures may be painful and lead to serious infections. Therefore, skin-smears should be limited to referral centres for special investigation and research purposes. (33)

#### Biopsy

Tissue biopsies are used to make a histologic diagnosis, to classify the disease and for research purposes. Biopsies can be taken from both skin and nerves. However, the biopsy cannot be regarded as the diagnostic gold standard since a number of them can be doubtful. (11)

#### Serology

Antibodies to the *M. leprae*-specific PGL-I are present in 90 % of patients with untreated lepromatous disease, 40-50 % of patients with paucibacillary disease and 1-5 % of healthy controls. (9) The antibody testing is specific and sensitive in patients with MB disease, but unfortunately it is not very helpful in the diagnosis of PB disease and is unable to predict, among contacts of known cases in the general population, who will develop the disease. This means that serology has little clinical value and so far the test has not played a significant role in the diagnosis of leprosy. (11)

## PCR

PCR for detection of *M. leprae* DNA encoding specific genes or repeat-sequences detects *M. leprae* DNA in 95 % of MB and 55 % of PB disease. (9) PCR is not available in every country, and in countries where it is available it has not proved, so far, to be as effective diagnostically as anticipated. (11) Currently PCR is not used in clinical practice. (9)

## **2.10 Treatment**

The main goals of treatment are (4):

- 1) Cure lesions.
- 2) Preventing irreversible nerve damage.
- 3) Preventing transmission of the bacterium.

Dapsone was discovered in the 1940s and became a cure for leprosy. But the treatment was life long and this was a challenge when it came to compliance. As time passed *M. leprae* developed resistance to dapsone, and this stimulated the search for new and efficient drugs. Rifampicin and clofazimine was introduced in the 1960s and 1970s (34), and in 1981 the WHO Expert Committee (13) recommended a combination of drugs (MDT) to prevent drug resistance. The combination consisted of rifampicin, dapsone and clofazimine. After the implementation of MDT in 1982, no multiple-drug-resistant organisms have been seen. Studies have shown that relapses that do occur after MDT are caused by drug sensitive *M. leprae*. (9) Since 1995 WHO has distributed MDT free of charge to all endemic countries. (35)

### 2.10.1 Treatment regimens

#### Adults

MB: 12 months

- Rifampicin 600 mg once a month
- Dapsone 100 mg daily
- Clofazimine 300 mg once a month + 50 mg daily

PB: 6 months

- Rifampicin 600 mg once a month
- Dapsone 100 mg daily

Single lesion PB: single dose of

- Rifampicin 600 mg
- Ofloxacin 400 mg
- Minocycline 100 mg

#### Children 10-14 years

MB: 12 months

- Rifampicin 450 mg once a month
- Dapsone 50 mg daily
- Clofazimine 150 mg once a month + 50 mg daily

PB: 6 months

- Rifampicin 450 mg once a month
- Dapsone 50 mg daily



For children under 10 year, the dose must be adjusted according to body weight. (26, 36)

Blister packs which contain all the tablets needed for one month are available. This helps the patients remember which medications have to be taken every day, and which should be taken once a month. This enhances the compliance and the treatment success.



**Figure 5:** Blister packs (26)

Although approximately 99.9% of leprosy bacilli are killed in about 3-4 months by dapsone and clofazimine, and within 3-7 days by single dose of rifampicin, there are cases where multibacillary patients relapse if they stop treatment. A small number of viable drug-susceptible *M. leprae* have been isolated from patients treated with rifampicin (as monotherapy or combined with tiambutosine). These bacilli, which are able to survive for many years in the patient despite the presence of bactericidal concentrations of an antileprosy drug, are called “persisters”. It is postulated that persisters are physiologically dormant bacilli and can thus escape the action of antileprosy drugs. It has been shown that persisters may survive for as long as 20 years in patients treated with dapsone monotherapy. (13)

### 2.10.2 Pharmacology

#### Rifampicin

Rifampicin is a potent bactericidal for *M. leprae*. (9) A single dose of 600 mg kills > 99,9% of the viable bacteria. (37) This mean that 4 days after a 600 mg dose, bacilli from a previously untreated patient are no longer viable in the mouse footpad test (9) and the patient is no longer contagious. (21) The medication acts by inhibiting DNA-dependent RNA-polymerase, and resistance to rifampicin is due to mutations in a region of *rpoB*. Rifampicin should always be given in combination with other drugs against leprosy to prevent the development of rifampicin resistance. (9) There has not been observed any toxic effects when rifampicin is administered once a month. (38) The urine may get a reddish colour after intake but this is harmless and disappears after some hours. (26)

#### Clofazimine

Clofazimine is weakly bactericidal, but the mechanism is unknown. It has an anti-inflammatory effect which has reduced the incidence of erythema nodosum reactions. (9) The medicine is well tolerated, but the skin may get a brown-black discoloration. This side effect disappears a few months after the completion of the MDT. (36)

Clofazimine is stored in the body after administration and is released slowly. By giving a dose of 300 mg once a month there will always be an optimal amount of clofazimine in the tissue even if the patient misses one of the daily doses. (37)

#### Dapsone

Dapsone is a sulfon and inhibits folic acid synthesis. (39) It is weakly bactericidal. (40)

#### Other drugs

Minocycline, clarithromycin, pefloxacin and ofloxacin are all efficient against *M. leprae*, but because of their high cost they are seldom used in field programmes. They can be used as second line drugs in

the case of dapsone allergy or if the pigmentation caused by clofazimine is unacceptable for the patient. (9)

### 2.10.3 Adverse effects.

Dapsone: Mild haemolytic anemia is common following treatment, but severe anemia is rare.

Rifampicin: Occasional cases of renal failure, thrombocytopenia, influenza-like symptoms and hepatitis have been reported.

Clofazimine: Pigmentation.

(18)

Some patients may be allergic to some of the drugs in MDT. The symptoms are itching and red/dark patches in the skin. In these cases the patient should stop taking the drugs and contact a hospital. (26)

## 2.11 Vaccines

Many anti-leprosy vaccines have been developed during the last century. Vaccination can be immunoprophylactic or immunotherapeutic. The immunoprophylactic aim is to restore the host recognition of shared mycobacterial antigens to promote Th1 responses and to induce CD8+ Tc-cells. The aim of immunotherapy is to switch off the mechanisms leading to immunopathology and to increase intracellular mechanisms by which bacilli are killed. (11)

The first vaccine used was the BCG vaccine. (11) Many randomized controlled trials and case-control studies showed that BCG vaccination gave variable protection against leprosy. (30) The protective effect varied from 20-30 % in Myanmar and India, to 80 % in Uganda. (18) Because of the BCG vaccine's failure to protect certain populations, the need for an improved vaccine against leprosy arose. (11) The addition of heat-killed *M. leprae* to BCG (Convit 1992) did not increase the protective effect of the vaccine in two trials in Malawi and Venezuela, but did in a large study in India. (9, 11)

Among other vaccines being used or explored are: Mycobacterium W (Talwar 1978), Mycobacterium ICRC (Deo et al. 1981), Mycobacterium tufo (Iushum and Kalianina 1995) and Mycobacterium Habana (Singh et al 1997). (11) None of these vaccines developed against leprosy have given a high level of protection. (30) The enthusiasm for use of vaccines has now lessened because of the significantly favourable impact of MDT on leprosy. (11) An ideal vaccine would be both a therapeutic agent (curing those already incubated) and a prophylactic agent (conferring a long-lasting immunity to leprosy infection). The development of a new leprosy vaccine has, however, not generally been regarded as a cost-effective venture. (23)

## 2.12 Epidemiology

Leprosy is most common in tropical and subtropical areas. The disease may however appear in Western countries because of immigration. (4)

In 1985 there were an estimated 12 million people with leprosy worldwide, i.e. a prevalence of 12 per 10 000. (9) The number of new cases of leprosy detected during 2007 was 254 525, and the global registered prevalence at the beginning of 2008 was 212 802. (2)

The table below shows the new cases detected (NCD) globally, excluding European Region, from 2001-2007. The annual detection has declined from 763 262 in 2001 to 254 525 in 2007. The registered prevalence has fallen from 458 428 in 2004 to 212 802 at the beginning of 2008.

	<b>NCD</b>	<b>Prevalence at start of year</b>
2001	763 262	
2002	620 639	
2003	514 718	
2004	407 791	458 428
2005	299 036	286 063
2006	259 017	219 826
2007	254 525	224 717
2008		212 802

**Figure 6:** New cases detected and prevalence. (2, 27, 41, 42, 43)

At the beginning of 2007, the United Republic of Tanzania achieved the goal of eliminating leprosy as a public health problem (43), i.e < 1 case of leprosy per 10 000 nationally. (44)

At the beginning of 2008, the Democratic Republic of the Congo and Mozambique reached the elimination goal. There are now three countries with a population > 1million that have yet to achieve the elimination goal. These countries are Brazil, Nepal and Timor-Leste and they account for about 17 % of the new cases detected during 2007 and 23 % of the registered cases at the beginning of 2008. There are 17 countries that during 2007 reported > 1000 new cases. These countries account for 94% of the new cases detected globally and are Angola, Bangladesh, Brazil, China, Democratic Republic of the Congo, Cote d'Ivoire, India, Ethiopia, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Nigeria, the Philippines, Sri Lanka and Sudan. (2)

Among countries with >100 new cases during 2007 there are great variations in terms of the proportion of newly detected cases with MB disease, of children and females and of those with grade 2 disabilities. In Ethiopia 92.93% of the new cases had MB leprosy in contrast to Somalia where 29.71% had MB leprosy. In Ecuador 18.69% of the new cases were females and in Lao People's Democratic Republic 77.60% were females. In the Comoros 37.96% were children and in China that number was 2.23%. In Micronesia 0% had grade 2 disabilities at the time of diagnosis but in Burundi 25.52% had already evolved such disabilities. (2)

### 2.12.1 Resolutions to eliminate leprosy

When the prevalence of leprosy decreased dramatically from the 1980s, WHO did began hoping that leprosy could be eliminated. WHO believed that it was the introduction of MDT that was the cause of the reduction in the prevalence. (45) At the 44th World Health Assembly (45) in 1991 a resolution to eliminate leprosy as a public health problem by the year 2000 was adopted. Elimination was defined as prevalence of < 1 case per 10 000 at the global level (45, 46).

The idea of elimination was based on the hypothesis that at a prevalence of < 1 case per 10 000 population the transmission of leprosy in the community would be interrupted (30), and the disease would die out. (45) By using the global population as the denominator, it was possible to declare the global elimination of leprosy achieved by the year 2000, (23) i.e. a world prevalence of less than approximately 600 000 leprosy patients. (34) The Strategic Plan 2000-2005 (44) had as its goal the elimination of leprosy as a public health problem, defined as reduction of prevalence to < 1 case per 10 000 nationally. The Global Strategy for Further Reducing the Leprosy burden and Sustaining Leprosy Control Activities 2006-2010 (27) is an evolution of the Strategic Plan, designed to address the remaining challenges and further reduce the leprosy burden. WHO admits that new cases of leprosy may occur even after reaching the elimination goal. But they explain this as a result of the long incubation period of leprosy, (45) and not as a result of continued transmission of infection. (47)

What are the causes for the decline in prevalence? Is the only cause the implementation of MDT? If it is, what are the hallmarks of MDT that enabled it to cause such a decrease?

## 3 Results and discussion

### 3.1 Development of multidrug therapy (MDT)

#### 3.1.1 Epidemiology before MDT

In 1970 the estimated number of leprosy cases were the same as in 1965 i.e. 10.8 millions (1) and this increased to an estimate of 12 million in 1985. (9)

According to WHO (1) some of the problems with the estimate in the 1970s was:

- The sensitivity of diagnostic criteria could vary according to detection procedures.
- Patients classified as lepromatous or borderline were regarded as potentially continuous sources of infection. This meant that all initially infectious cases were considered as active and were included in prevalence rates.
- Failure to distinguish clearly between active and inactive disease.
- Time lag in releasing from control tuberculoid cases that fulfilled the criteria recommended for release.

#### 3.1.2 Treatment before MDT

The standard drug in the 1970s was dapsone, given as parenteral or as tablets, in the dose of 6-10 mg per kg body weight per week. This dose amounted to 50-100 mg daily in full size adults. It was known that dapsone was not an ideal drug against *M. leprae* as it took more than 5 years of continuous therapy to render most of the patients with lepromatous leprosy bacteriologically negative. Relapses were known to occur. (1) However, in the early 1970s there was no established alternative drug for leprosy treatment.

In the 1976 WHO report (48) it was stated that dapsone resistance had become a major problem. It seemed that the appearance of drug resistance was related to very low initial doses, low-dose maintenance therapy and irregular treatment. It was secondary resistance, i.e. bacteria in an already infected patient gained resistance, that had become increasingly common in lepromatous (LL) and borderline (BL) cases. Proven primary resistance, i.e. where the patient had been infected with an already resistant bacteria, had yet not been reported.

In order to prevent secondary dapsone resistance new guidelines for treatment of newly diagnosed cases were made: Generally, dapsone should be commenced and maintained in full dosage, treatment should be continued regularly without interruption and initial combined therapy should be given to lepromatous (LL) and borderline (BL, BB) cases.

Dapsone remained the basis of treatment, in the dosage of 6-10 mg/kg body weight per week. If dapsone injection was preferred the dosage was 300-400 mg twice weekly or 600 mg once a week. In bacteriologically negative tuberculoid (TT, BT) and indeterminate adult patients a dose of 50 mg dapsone daily was sufficient. In addition to dapsone, clofazimine was to be given in the dosage of either 100 mg daily or 100 mg three times a week for the first 4-6 months to patients with LL og BL. After 4-6 months the patients would continue with dapsone in unchanged dosage. An alternative regimen would be dapsone combined with rifampicin. It was then suggested that rifampicin would be given in the dosage of 300-600 mg daily for a minimum of 2 weeks. (48) In the case of dapsone resistance 600 mg rifampicin daily and 100 mg clofazimine daily would be given for a duration of 2-3 months followed by indefinite use of clofazimine. (48)

Until the mid-1970s virtually all strains of *M. leprae* isolated in mice from previously untreated patients were inhibited from multiplying by the administration of 0,1 mg dapsone per 100 g of food in the diet, i.e. they were not primary resistant to dapsone. In 1976 one had not yet seen primary dapsone

resistance, but in 1977 Pearson et. al reported that 5 of 8 randomly selected newly diagnosed cases of lepromatous leprosy in Ethiopia were found to be infected with dapsone-resistant strains of *M. leprae*. Primary dapsone resistance was found other places as well. (13) The number of countries with secondary dapsone resistance was in 1982 over 25, and increasing. Low-dosage dapsone therapy and irregular treatment predisposed patients to develop resistance. (13)

Rifampicin was often used for limited periods of time in the initial intensive phase of multidrug therapy of newly diagnosed cases of multibacillary leprosy. In Malaysia and in Carville, LA in the US, rifampicin had been used for long-term monotherapy treatment in lepromatous patients with dapsone resistance. In Carville there were found rifampicin resistant strains. (13)

Clofazimine was used both to treat erythema nodosum leprosum and to treat dapsone resistant patients. Despite its widespread use one had not been able to prove clofazimine resistance. (13)

### 3.1.3 Why MDT

In 1976 the WHO expert committee on leprosy recommended new treatment regimens to prevent drug resistance. In 1982 WHO stated that only a few countries and individual centres had introduced the multidrug therapy as a routine practice in their leprosy control programmes. (13)

Why had not every country implemented the recommendations? The study group of leprosy (13) found several reasons:

- 1) First there was the problem with failure to perceive the urgency of the situation. One seemed to believe that dapsone monotherapy was enough and did not really understand the threat posed by dapsone resistance.
- 2) Then there was the insufficient recognition of the problem with compliance. The dapsone treatment lasted for several years and unsupervised self-administered chemotherapy would often not be adhered to for this long period. The drop-out rates were high and investigations showed that even patients who collected the drugs regularly did not necessarily ingest them. Due to fear of relapse treatment was often continued indefinitely even in cases that met the criteria for release from control. This contributed to the poor compliance and put unnecessary pressure on leprosy clinics when it came to time and resources.
- 3) There was frequently reluctance in control programmes to undertake the revisions needed to carry out the recommendations of the expert committee:
  - Primary health care workers would need to be adequately trained to make a tentative diagnosis of leprosy. There had to be improvement of the bacteriological examination techniques, contact surveillance of households with a lepromatous patient and better case detections through examination of schoolchildren and contacts of known cases. In addition, efficient outpatient treatment in convenient health centres and health education of patients, families, teachers, social workers and members of the medical professions were needed as well. (48)
  - Combined chemotherapy with more potent, more toxic and more expensive drugs required closer supervision than dapsone monotherapy and this appeared to present insurmountable problems to many control programmes. In addition, new activities could not readily be incorporated into the existing control programmes which were already stretched to the limit in terms of manpower and finance. (13)
- 4) There was some uncertainty with regard to the recommended combined therapy of rifampicin and clofazimine, and there was fear of toxicity and other complications associated with such therapy. (13)

### 3.1.4 Recommended treatment

The Study Group (13) did in 1982 decide on a new recommended treatment. There were two main objectives with the treatment:

- 1) Interrupt the transmission of the bacteria between individuals.
- 2) Cure the patient.

By the use of MDT one also sought to prevent the emergence of drug-resistant strains, as organisms that were resistance to one drug would often be killed by drug number two or three.

#### 3.1.4.1 Multibacillary leprosy

All patients were to get the same treatment. This included newly diagnosed untreated patients, patients who had responded satisfactorily to previous treatment, patients who had not responded satisfactorily to previous treatment and patients who had relapsed while on treatment. (13)

4 drugs were recommended. Only bactericidal drugs were to be used. (13) It was recommended that the treatment should consist of at least two drugs in addition to dapsone. Because of rifampicins great potency it should always be one of the two additional drugs.

Standard dosages:

Rifampicin	600 mg once monthly, supervised
Dapsone	100 mg daily, self-administered
Clofazimine	300 mg once monthly, supervised and 50 mg daily, self-administered

Dosages should be adjusted to the weight of the patient.

Clofazimine were to be replaced by 250-375 mg self-administered daily doses of ethionamide/protionamid if the coloration of the skin were unacceptable to the patient. (13)

The duration of the combined therapy was at least 24 months and to be continued up to smear negativity. (13) In 1993 the WHO study group(17) changed the recommended duration of MDT treatment for MB leprosy to 24 months rather than to smear negativity. According to the 7th report from WHO Expert Committee on Leprosy in 1998 (18) the treatment length could again be reduced, and was then made to be 12 months.

#### 3.1.4.2 Paucibacillary leprosy

Even though a large number of patients with single lesions heal spontaneously all paucibacillary patients were to be treated because it was impossible to distinguish those that would heal from those that would not. (13)

Standard dosages:

Rifampicin	600 mg once monthly, supervised
Dapsone	100 mg daily, self-administered

The duration was 6 months. All newly diagnosed PB patients, all dapsone-treated PB patients who relapsed and PB patients who were on treatment with dapsone monotherapy and had not yet completed two years of treatment were to be treated with this regimen. (13)

In the 7th report from WHO Expert Committee on Leprosy (18) in 1998 it was recommended that patients with single-lesion PB leprosy were to be treated with a single dose of a combination of rifampicin, ofloxacin and minocycline.

### 3.2 Decline in prevalence since the 1970s

Since the introduction of dapsone in the early 1950s, patients have been registered in treatment programmes to promote adherence. Numbers of patients on treatment are reported and data are

collected to produce national and global prevalence statistics. (18, 23)

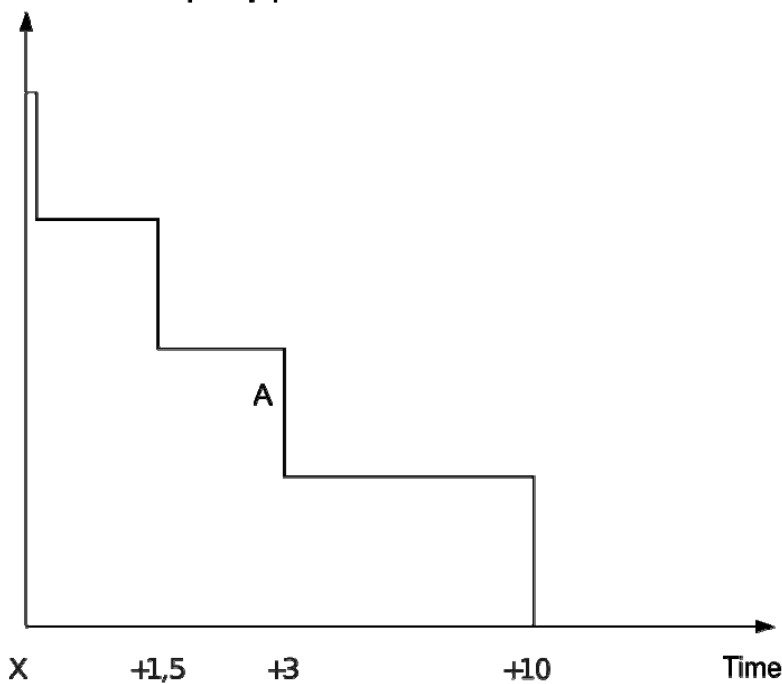
Prevalence numbers are used to measure progress of the leprosy burden. For measuring the burden of leprosy WHO finds that prevalence at the end of the year (per 31st of December) is a simple and easily understandable indicator. (28, 33)

### 3.2.1 Inactive cases and release from control

In WHO's Expert Committee on Leprosy of 1970 (1) new definitions for "inactive cases" and "release from control" were proposed. A leprosy patient without any sign of clinical activity and with negative bacteriological findings was considered as an inactive case. Once inactivity was achieved, regular treatment was to be continued for varying periods of time before the patient was released from control. These periods were 1 ½ year for tuberculoid, 3 years for indeterminate and at least 10 years for lepromatous and borderline cases.

Not everywhere had there been taken action to identify treated cases as inactive. At these places tuberculoid patients without any signs of clinical activity and with negative bacteriological findings could be directly released from control provided they had been regularly treated for at least 5 years and the decision was taken by a doctor or by the senior auxiliary staff. (1)

**Number of leprosy patients**



**Figure 7:** The graph shows the fall in the number of registered leprosy patients that were classified as inactive at time X.

With the introduction of this norm, a decrease in leprosy prevalence happened. In figure 7 curve A shows how the number of inactive patients would decrease in a specific area when the norm is applied. The first decrease is caused by deletion from registers those patients that did not have any signs of clinical activity or bacteriological findings at time X and had been regularly treated for leprosy for at least 5 years. The next decrease will be when tuberculoid patients are deleted from registers 1 ½ years after being classified as inactive cases. 3 years after the implementation inactive indeterminate patients are deleted from registers and another fall in prevalence is seen. After 10 years, when inactive

lepomatous and borderline cases are deleted from registers, the fourth fall is seen. If the norm had been put into place simultaneously world wide the global number of inactive cases would decrease dramatically, similar to curve A, during a 10 year period.

### 3.2.2 Introduction of MDT

Even though MDT was recommended in 1982 the regimen was initiated very slowly. In 1986 8.77% of registered cases were given this therapy. This increased to 32.7% in 1988, 55.7% in 1990 and in 1998 MDT was given to >99% of leprosy patients. (49, 50) Currently 100 % of registered cases are receiving MDT (51).

As the MDT coverage increased, more and more patients got a fixed treatment length which meant that their treatment one day would come to an end and the patients were to be deleted from registers. When patients are deleted from registers, prevalence numbers will necessarily decrease. The gradual implementation of MDT world wide implied that patients in one area were still using the old treatment, while in other areas patients used the new recommended treatment and treatment length. As a result of this, the reduction in prevalence number globally did not fall abruptly but rather slowly.

### 3.2.3 Changing the length of treatment

In the dapsone era patients were treated for years. By the introduction of MDT in 1982 the duration of treatment was reduced to 24 and 6 months for MB and PB leprosy respectively. This led to a remarkable reduction in prevalence since patients that were cured after MDT, and did not require further surveillance, were deleted from registers. Further reduction in treatment length for MB patients from 24 to 12 months in 1998 led to a halving of the prevalence number for this group. When WHO at the same time reduced treatment length for PB patients with single lesions from 6 months to one day this also contributed greatly to the prevalence reduction.

When the duration of treatment decreases below one year, the time of year in which a patient is being treated will also affect the prevalence number. Patients with single skin lesions account for a significant proportion of newly diagnosed cases. The proportion varies from 20-30% in Malawi to close to 60% in India. (18) The treatment of these patients is a single dose of a combination of drugs. Most of these patients will not be receiving treatment at the 31st of December, and are therefore not contributing to the prevalence number. Neither PB-leprosy patients who receive their 6 months course of MDT early in the calendar year, and hence have finished their treatment before the end of the year, are contributing to the prevalence number.

Consequently, the widespread introduction of MDT and subsequent fixed duration of treatment led to a dramatic reduction in the registered prevalence as patients were deleted from registers when they finished their treatment. With the reductions in treatment length some years later, new drops in prevalence were seen.

### 3.2.4 Definitions of leprosy

In the sixth report from WHO Expert Committee on Leprosy (15), published in 1988, a new definition of a "case of leprosy" was made. Previously patients needing or undergoing treatment, those who had completed multidrug therapy and required/were under surveillance as well as those with deformities and disabilities resulting from leprosy and needing care were grouped together as cases of leprosy. The new definition was "a person showing clinical signs of leprosy, with or without bacteriological confirmation of the diagnosis, and requiring chemotherapy". At the same time WHO stated that prevalence of leprosy should be computed on the basis on those requiring or receiving chemotherapy.



In 1998 a new definition by WHO (18) stated that a case of leprosy was a person having one or more of the following features and who had yet to complete a full course of treatment:

- Hypopigmented or reddish skin lesion(s) with definite loss of sensation.
- Involvement of the peripheral nerves, as demonstrated by definite thickening with loss of sensation.
- Skin smear positive for acid-fast bacilli.

This definition included patients who had started MDT but who had not received treatment for 12 consecutive months (defaulters) and who had signs of active disease such as new skin lesions, new nerve involvement and new nodules. It also included patients who relapsed after completing a full course of treatment.

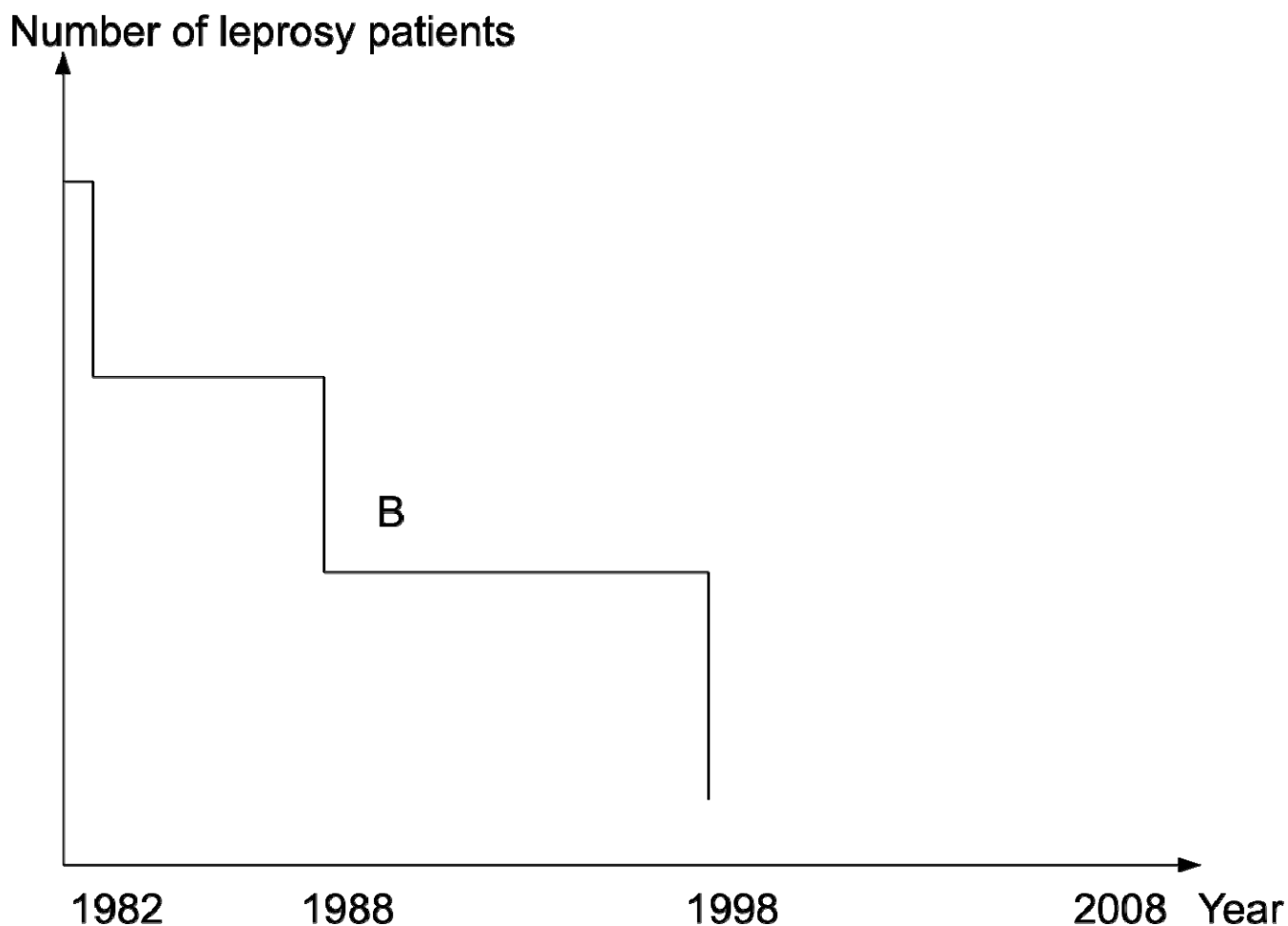
In addition, the definition of prevalence was changed to “the number of leprosy cases registered for chemotherapy”

Each time new diagnostic criteria are implemented, the prevalence number ought to change accordingly.

When WHO in 1988 redefined which patients were to be registered as cases of leprosy the new definition no longer included those who had completed MDT but still were under/required surveillance, nor patients with disabilities due to leprosy. By narrowing the definition, the patients mentioned above were excluded which resulted in a decrease in leprosy prevalence.

The new prevalence definition in 1998 meant that patients who were diagnosed, but had not yet started treatment, were not included in the registers. Depending on the amount of time from diagnosis to start of treatment, this delay could contribute to misleading prevalence number.

When only patients under treatment with MDT are being included in the reported prevalence numbers, one loses the cumulative prevalence of previous patients with persistent disabilities. People with deformities as a result of leprosy need further surveillance and treatment, all of which require resources. When it seems that leprosy is no longer a problem due to the reduction in prevalence number, some may believe that there is no longer need for money and resources. In 1998 the global estimate of people with leprosy-related impairments and disabilities was 3 million, of which 2 million had grade 2 disabilities and 1 million had grade 1 disabilities. (18)



**Figure 8:** Summary of 3.2.2-3.2.4

1982: Introduction of MDT and treatment length decreases from lifelong to 24 and 6 months for MB and PB leprosy respectively.

1988: New definition of a case of leprosy and new definition of prevalence.

1998: New definition of a case of leprosy, new definition of prevalence and treatment length reduced from 24 months to 12 months for MB leprosy and from 6 months to one day for patients with single skin lesion.

Curve B shows how prevalence would fall if the changes had been implemented at the same time worldwide.

### **3.3 NCDR vs prevalence**

We have already discussed that registered prevalence are affected by the duration of treatment. In recent years attention has turned to the new case detection rate (NCDR) as a proxy for the incidence of leprosy. This was felt to be a more accurate reflection of the epidemiologic position than the registered prevalence. (23) NCDR is not affected by the duration of treatment. Because incident cases might be the ones transmitting the disease, NCDR would be a better indicator of the remaining potential for transmission in the community. In the dapsone era, incidence would have to be very low for the prevalence to be as low as 1 in 10 000, so transmission would be minimal. After the introduction of MDT and the shortened duration of treatment, incidence can still be relatively high, even when the prevalence has been reduced to target level. (23)

Trends in NCDR reflect trends in incidence rates, provided that no significant changes occur in case detection efforts, self-reporting behaviour, or diagnostic procedures or criteria. (34) Operational

influence is particularly visible in India, where NCD dropped by 66% from 407 791 in 2004 (41) to 139 252 in 2006 (43). While the proportion of new cases with WHO grade 2 disability increased by 38% between 2004 and 2007. This increase suggests less active case finding. Dramatic drops within a short period of time are not credible biologically because of the long incubation period of leprosy and the absence of an instantaneously implemented high-coverage preventive intervention such as vaccination in the decade preceding the sudden drop in case detection. (34)

### **3.4 Can we trust the prevalence numbers?**

Once a year WHO publish an overview of the global leprosy situation, excluding the European region. In the report published in 2007 (43) data from 109 countries or territories are listed. Out of these countries/territories 82 did report a prevalence of leprosy of  $\geq 1$  per 10 000 at the beginning of 2007 and 97 reported newly detected cases  $\geq 1$  per 10 000 during 2006.

One also gets the number of new MB cases in every country/territory. Since all MB patients are to get 12 months of MDT one would assume that patients detected during 2006 would contribute to the prevalence at the beginning of 2007. However, this is not always the case. Colombia had 398 newly detected cases during 2006 out of which 286 was MB cases. But Colombia does not report any prevalence number. In the United States of America 72 new cases of MB are reported, but they have also neglected to report any prevalence. Neither is there information available about the prevalence in Myanmar at the beginning of 2007, this field is blank. New cases detected during 2006 were however 3721, and 2345 of these was MB leprosy. Similar examples of discrepancy between NCD and registered prevalence can be described from Iran, Somalia and Yemen among others.

What is the explanation for this discrepancy between NCD and registered prevalence? What is the reason for this underreporting of prevalence? Does this mean that WHO's statistics are not trustworthy? If data is not correct, how can one state that elimination of leprosy is attained?

### **3.5 Who are the source of transmission?**

Since the discovery of *M. leprae* in 1873, the transmission of the disease has remained a mystery. For many years scientists have believed that patients with lepromatous leprosy were the main source of transmission. Untreated patients with this form of leprosy do carry a large bacterial load in their nasal epithelium. (6) Therefore it is obvious that these patients may shed bacteria that can infect healthy individuals. The longer it takes before a lepromatous case is detected and started on MDT the longer there is for infection to spread from this person. Even though PB patients carry a much smaller load of bacteria (22) one can not rule out the possibility that they also contribute to the spread of infection.

Studies (24) have documented that the bacteria may survive outside human for as long as 60 days. This has suggested that indirect spread of infection may be a possibility. Transmission via insects, animals or even healthy carriers has also been postulated.

WHO claims that if patients with signs and symptoms of leprosy are being treated with MDT the transmission of *M. leprae* will cease and there will be no new leprosy cases (47). But what about subclinical infection? As many surveys have found (24): healthy persons carry *M. leprae* DNA and *M. leprae* in their nasal cavities. One can not rule out that these people also transmit the bacteria and in this way contribute to the spread of the disease.

How long does it take from a person gets infected, develop clinical signs of disease and ultimately get MDT? As previously mentioned, the average incubation period is 4 years in tuberculoid leprosy and 10 years for lepromatous leprosy. If we assume that patients get treatment at once when clinical signs appear, there are still many years where they have a subclinical infection and where the possibility for spread of the bacteria is present.

It was assumed that introduction of MDT would decrease transmission. Although the registered prevalence has shown a dramatic reduction after the widespread introduction of MDT, global incidence has decreased much less. Thus, there is little evidence that the underlying epidemiology of leprosy has changed since the introduction of MDT. This unexpected failure of leprosy control programs using rifampicin containing regimens to reduce transmission suggests that transmission must be occurring early in the course of the disease, before diagnosis and the start of treatment, perhaps even during the later stages of incubation, before the onset of clinical signs and symptoms. (23)

### **3.6 Active case finding in two areas in India**

A paper published in Leprosy review in January 2009 (52) was built upon a study performed to estimate the prevalence of undetected active cases of leprosy in the community. One rural and one urban area were investigated. The prevalence rates in these areas, published by the government of India, were 1.37 and 0.9 per 10 000, respectively. The investigation was done primarily with a house-to-house survey from June to September 2007.

In the rural area 90.8 % of 0.2 million inhabitants were examined. 120 active cases were detected (6.92/10 000) and of these 97 underwent clinical examination and were confirmed to leprosy. Of these 90 were newly detected leprosy cases, which gives a prevalence of 5.04/ 10 000. 34.37% were children < 14 years (15.62 % of the children were  $\leq 5$  years). A total of 18% had disabilities grade 1 or 2.

In the urban area 85% of the population of 0.6 million were examined. 134 active cases were detected. (2.61/10 000) of which 116 underwent clinical examination, leading to 109 new cases of leprosy detected and a prevalence of 2.13/10 000. 38.88% were children. (13.89 % of the children were  $\leq 5$  years). A total of 17% had disabilities grade 1 or 2.

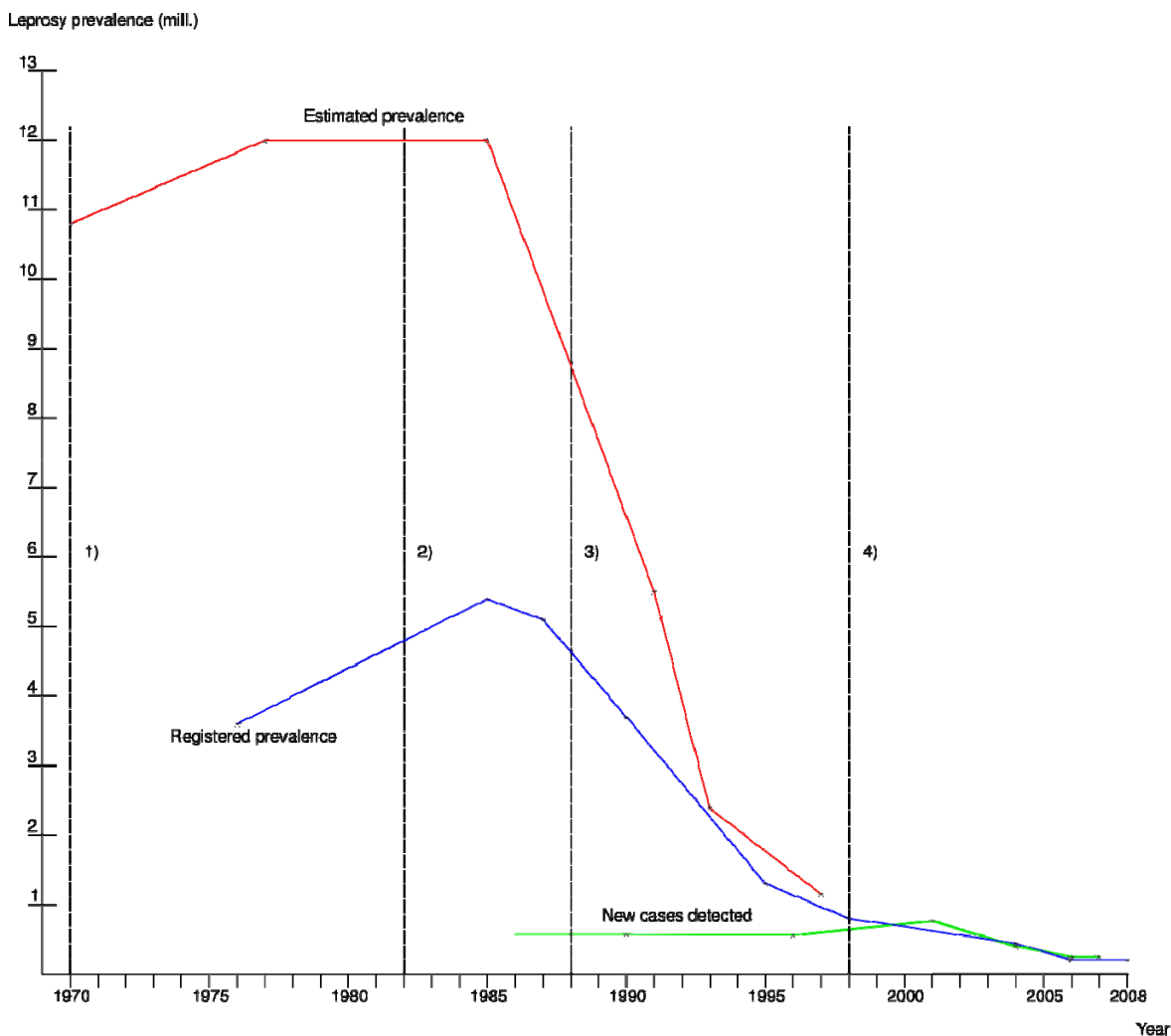
Smear examination were performed on 182 cases: 13% (24/182) were positive, all of which had > 5 skin lesions. 75% of these had BI  $\geq 3+$ . All PB and pure neural cases were negative. Biopsy was taken from 138 patients. 12.5% of single skin lesions (SSL) showed features of BB-BL type, indicative of high risk of transmission.

Since the government of India does not include SSL cases as leprosy cases the SSL were excluded in prevalence numbers. This leads to a prevalence in the rural area of 3.63/ 10 000 and 1.22/10 000 in the urban area, both of which are higher than the numbers reported by the government.

The survey thus reveals that there are large numbers of previously undetected leprosy cases in the study population. The authors refer to studies from Bangladesh and Brazil which also shows that the prevalence of previously undiagnosed leprosy cases is higher than the registered one. They state that the high proportion of smear positive leprosy patients, high proportion of grade 2 deformity and high burden of leprosy in children implies likelihood of an extended active transmission of leprosy in the community. A large proportion of individuals with leprosy had never heard about leprosy before the survey was conducted. And a high percentage of patients had not sought care for leprosy for over a year after appearance of initial symptoms of leprosy.

### 3.7 Conclusion

The global registered prevalence has indeed fallen dramatically since the 1970s and especially since the introduction of MDT in the 1980s. Numbers has decreased from an estimated 10.8 million in 1970 to 5.3 million registered in 1986 (49), 0.8 million registered cases in 1998 (50) and a further reduction to 0.2 million registered cases in 2008 (2). This fall can to a great extent be explained by operational changes, i.e. definition of inactive cases and subsequently release from control, reduced treatment length, time of year for the registration of prevalence and changing definitions of a case of leprosy and prevalence, and not by a reduced transmission of *M. leprae* as a consequence of the introduction of MDT per se.



**Figure 9:** registered leprosy cases, estimated leprosy cases and new cases detected since 1970 based on data from 1, 2, 9, 15, 16, 18, 41, 42, 43, 48, 50, 53, 54, 55, 56 and 57.

The graph shows curves for registered leprosy cases per 31st of December each year, estimated leprosy cases and new cases.

Four years are marked out where changes were made regarding inactive cases and release from control 1), introduction of MDT 2), changes in definition of leprosy and prevalence of leprosy 3) and finally changes in definition of leprosy, prevalence of leprosy and reduction in treatment length 4).

We see that the drops in estimated and registered prevalence correspond to a great extent to when the changes were made. Even though the prevalence has decreased, the number of new cases detected each

year has been rather static, implying that the transmission of leprosy has not been affected to the same degree.

By using the registered prevalence as a measurement of the leprosy burden, instead of NCD/NCDR, one only gets the number of patients on treatment per 31st of December. In this way one loses the actual number of new patients detected, i.e. the indicator of the remaining potential for transmission. In addition, the global prevalence number estimated by WHO is somewhat uncertain because of the incomplete and therefore misleading reporting from affected countries. Even though there are not reported any cases of leprosy, this does not mean that there are no leprosy cases. The paper from Shetty VP et al. (52) is a good example of this last statement. In this study they did house-to-house visits where they examined almost everyone in two districts in India for signs of leprosy, and found a far greater prevalence of leprosy than was reported from the government. According to the paper, many of those that got the diagnosis of leprosy after this examination claimed they had never heard about leprosy before, and because of that did not seek help for their skin lesions or nerve involvement. Since 1985 to date, > 15 million people have been detected and cured with MDT. (51) This has prevented many from develop irreversible deformities. However, there are still many new cases of leprosy detected each year. These cases are not considered as true new cases by WHO, but rather a result of infection acquired many years earlier. (44)

Since the transmission of *M. leprae* is still somewhat uncertain, and one yet are unsure throughout which period of incubation and clinical disease a person is most infectious, there are still unanswered important questions to investigate.

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