EVALUATION OF INTERVENTIONS TO PREVENT DISABILITY IN LEPROSY

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COLOFON

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‘Vertrouw bij je werk op de HEER,
en je plannen zullen slagen.’
(*Spreuken 16:3; Nieuwe Bijbelvertaling*)

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CHAPTER 1

General introduction

"I was rereading a favourite article, "A Short History of Leprosy in Postage Stamps", when I suddenly wondered what the average person thought leprosy was. I asked a random passer-by (okay, my daughter) and she said something along the lines of *'their hands and legs fall off, and sometimes even their heads'*. I'm sure she meant their noses, rather than their heads. However, like many of us, she believed that leprosy caused bits of your body to fall completely off – but that's not true." [1]

I. GENERAL BACKGROUND

What is leprosy?

Leprosy is an infectious disease dating back to ancient times before Christ. Most likely, the infection spread slowly from Asia to Europe and from there to the Americas, Australia and New Zealand. In Europe, the number of infected people reached its peak in the 13th century. After the 16th century, leprosy was on the decline over most of Europe and the number of people affected by leprosy fell rapidly [2,3]. Nowadays, many people only know leprosy from stories, pictures or books since the disease has become less and less prevalent.

Cause

Leprosy is caused by the bacillus *Mycobacterium leprae*. Leprosy bacilli are most probably spread through tiny droplets from the nose or mouth from infected and untreated individuals. Most people will never know that they have been infected because their immune system functions well. But when the immune system fails to respond effectively to the antigens of the bacilli, the disease will develop. The time between infection and the first visible signs of leprosy varies greatly and is usually between two and twelve years, but sometimes more than 20 years [4,5].

Signs, symptoms and classification

To confirm whether a person has leprosy, at least one of three signs should be found during a clinical examination: loss of feeling in typical skin patches, enlargement of peripheral nerves and the presence of leprosy bacilli in a skin smear [4]. In the early stage of leprosy, called indeterminate, one or few unusual spots or patches on the skin may occur. Often the disease heals spontaneously, but sometimes the disease progresses to an advanced form. This depends mainly on how the immune system of an individual responds [6].

Ridley and Jopling described a spectrum of leprosy forms, known as the Ridley-Jopling classification [7]. At one end of this spectrum is the tuberculoid form (TT) of leprosy. People with this form have a strong immune response resulting in few signs and symptoms of the disease. They often have only one or very few well-defined skin patches and a low number of bacilli in their body. At the other end of the spectrum is the lepromatous (LL) form of leprosy. People with this form have no or very little immune resistance and present with skin patches all over the body and harbour many bacilli. Most people have one of the intermediate forms of leprosy: borderline tuberculoid (BT), mid-borderline (BB), or borderline lepromatous (BL). These forms are less easy to distinguish and less stable, meaning that one can shift from one form to another [6,8]. This may happen during so-called reactions, which will be described below.

The Ridley-Jopling classification is very useful for prognosis and treatment of leprosy. For example, people with borderline leprosy have a much higher risk of developing reactions than people with tuberculoid leprosy, and the lepromatous form needs longer antibiotic treatment than the tuberculoid form [9]. In practice, it may be difficult to determine the form of leprosy according

to the Ridley-Jopling classification. To make decisions about treatment easier, The World Health Organization (WHO) developed an additional simplified dichotomous classification, paucibacillary (PB) leprosy or multibacillary (MB) leprosy. Currently, people with five or less skin lesions are classified as paucibacillary (PB) leprosy, while people with six or more skin lesions are classified as multibacillary (MB) leprosy [10].

Reactions are periods of inflammation in the skin and nerves. They are caused by the body's immune response to the antigens of the leprosy bacilli. Inflammation in nerves may result in loss of function due to swelling and pressure in the nerve. Reactions are the main cause of acute nerve damage and disability in leprosy and occur in about 10-30% of people with leprosy [11]. There are two types of reactions. Type 1 reaction or reversal reaction (RR) is a delayed or increased immune response resulting in acute inflammation in existing skin lesions and in peripheral nerves. The inflammation is usually confined to skin and nerves [12]. This type of reaction may occur at any time during the disease, but most often within the first six months of antibiotic treatment, however it may also occur years after treatment [13]. It is only seen in people with borderline leprosy and occurs in about a quarter of these people [14]. Type 2 reaction or erythema nodosum leprosum (ENL) is a reaction to circulating immune complexes in the blood. New, red and painful nodules in the skin appear. ENL is systemic and other organs but the skin may be affected, such as eyes and joints. People often feel ill due to fever and general malaise. ENL usually occurs first during treatment and often more episodes follow, making it a chronic condition. ENL is only seen in people with lepromatous (BL or LL) leprosy, and the proportion experiencing ENL varies from about 5% to almost 50% [14,15]. Figure 1 shows an overview of the Ridley-Jopling classification and reactions.

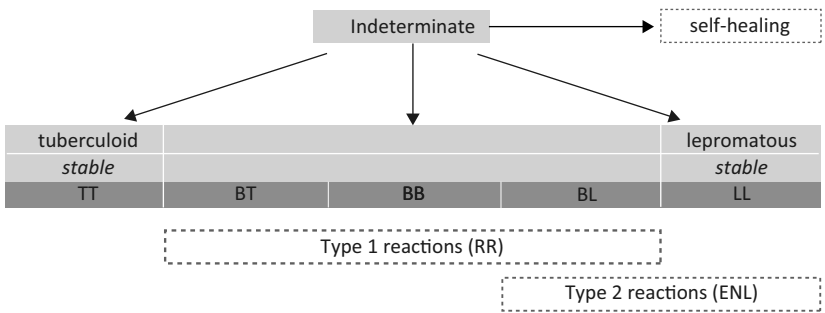

Figure 1. Ridley-Jopling leprosy classification and reactions

Epidemiology

In 1991, the WHO set the target of eliminating leprosy as a public health problem by the year 2000 [16]. The elimination campaign of the WHO resulted in increased efforts of countries to make communities aware of leprosy, to find new cases and to provide antibiotic treatment. Between

1985 and 2004 more than 13 million people were cured and the number of registered people had fallen by almost 90% [17]. Although the WHO target was achieved at the global level by the end of 2000, several countries still have not reached this goal at national level [18].

The elimination campaign, and especially the definition used for elimination, has raised much discussion. A conventional definition of elimination of a disease is the reduction to zero of the incidence of a specified disease in a defined geographical area as a result of deliberate efforts [19]. The latest WHO statistics show that the detection of new leprosy cases is ongoing. In 2007, about 258,000 new cases were detected [20]. Instead of achieving elimination of leprosy, resulting in a reduction to zero of the incidence, the WHO targeted control of leprosy, defined as the reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts [19,21]. Another point of discussion has been the definition of a leprosy case. Only people registered for antibiotic treatment on 31 December of a calendar year are counted, meaning that people in need of other treatment or care for complications or disability, or people who completed a single-dose or 6-month antibiotic treatment before the end of the year are not included. Also, the duration of treatment for people with MB leprosy changed from 24 months to 12 months and halved the prevalence of this group. The drop in prevalence therefore reflects in part the shortened treatment duration [22]. Achieving elimination of leprosy according to the conventional definition requires more than control. First of all an effective intervention is needed to interrupt the transmission of the leprosy bacillus [21].

Treatment

If recognised early, leprosy can be treated easily and it will not cause the disabilities that most people think of whenever they hear the word 'leprosy' [4]. Leprosy infection can be treated effectively with a combination of several antibiotics (dapsone, rifampicin, clofazimine), called multidrug therapy (MDT). In general, patients with PB leprosy receive treatment (dapsone and rifampicin) for six months and those with MB leprosy are treated with dapsone, rifampicin and clofazimine for 12 months [18].

Consequences

More than most other diseases, leprosy has a very negative image. People affected by leprosy fear stigmatization and discrimination. In the past, 'lepers' were regarded as unclean and highly contagious. They were often sent to isolated houses or colonies and in Europe they had to carry a warning bell or clapper [3,23]. Wrong beliefs about leprosy and social exclusion still seem very difficult to eliminate.

Leprosy is a disabling disease. Acute nerve damage may cause loss of feeling and muscle weakness, especially in the hands, feet and eyelids, called primary impairment. If untreated, this may lead to secondary impairment, such as unintentional wounds, ulcers, contractures of fingers and toes, blindness and deformity [14].

II. DISABILITY

Definition of disability

The concept of disability has changed remarkably over the past decades. In 1980, the International Classification of Impairments, Disabilities, and Handicaps (ICIDH), developed by the WHO, was published as a framework to classify consequences of ill health in terms of impairments, disabilities and handicaps. Impairment was defined as "any loss or abnormality of psychological, physiological or anatomical structure or function' and disability as 'any restriction or inability (mostly resulting from an impairment) to perform an activity in the manner or within the range considered normal for a human being" [24]. In the 1990s, this classification has been revised and the new version was published in 2001 as the International Classification of Functioning, Disability and Health (ICF). The main difference between the two classifications is that the ICF takes into account the effects of interaction between personal factors, environmental factors and health conditions on functioning and disability. Disability is no longer seen only as a result of physical impairment, but the new concept covers impairments, activity limitations and participation restrictions [25]. A proposed new definition of disability is: "difficulty in functioning at body, person or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors" [26]. Figure 2 shows the 'dynamic' ICF model of functioning, disability and health.

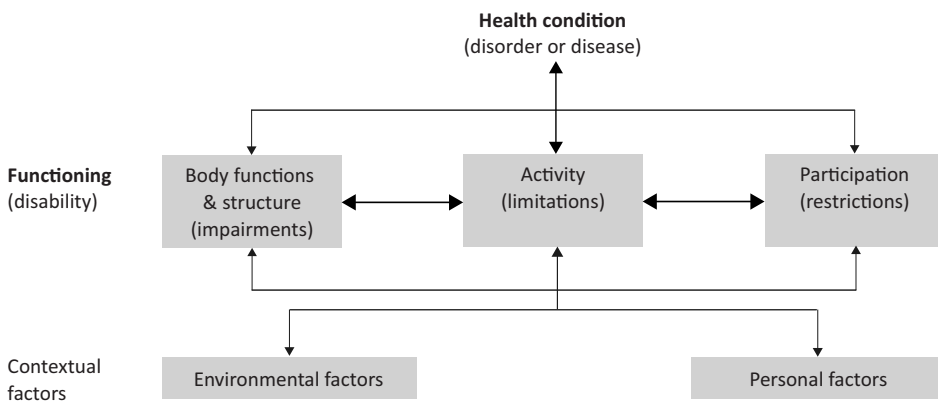

Figure 2. ICF model of functioning, disability and health

Burden of leprosy disability

Leprosy is a leading cause of permanent physical disability among infectious diseases [27]. In 2004, the WHO reported that "although MDT has had a dramatic impact on global prevalence, there are still two to three million people with deformities worldwide" [17]. But leprosy causes more than

physical disability. Being 'disabled' as a person in daily life through stigmatization and discrimination is often experienced as a far worse consequence of leprosy. Many people affected by leprosy, especially those with visible disability, may experience severe social, economic and psychological problems, such as divorce, unemployment, exclusion from social activities, rejection of family and community, and mental distress [28,29].

Prevention of disability (POD)

An important overall aim of leprosy control programmes is to prevent disabilities. Prevention of disability (POD) in leprosy has mainly focused on preventing permanent impairment, reversing impairment, and preventing further impairment and disabilities. POD activities aimed at preventing permanent disability include early detection and treatment of acute nerve damage and reactions. Interventions for preventing worsening of established disability are for example, self-care of impaired eyes, hands and feet and provision of appropriate assistive devices or footwear and reconstructive surgery [30]. With the current broader definition of disability, POD in leprosy may be better defined as 'a concept comprising all activities at individual, community and programme level aimed at preventing impairments, activity limitations and participation restrictions' [11]. This includes also activities which help people to rehabilitate socially and economically, such as counselling, education, vocational training and advocacy [31].

Early detection and assessment of nerve damage

Disability due to leprosy is preventable. The key to prevention of disability is early recognition, diagnosis and treatment of leprosy infection and acute nerve damage [32-34]. Nerve damage may develop slowly or without overt signs. It is often the symptoms of a reaction (e.g. inflamed skin patches, tender nerves, nerve function impairment) that force people to seek help [35,36]. People are often unaware or ignorant of the early signs and symptoms of leprosy. This is an important cause for delay in diagnosis and treatment. Further delay may be caused by consulting practitioners in traditional and alternative medicine, misdiagnoses, stigma, and costs and accessibility of health services [37-39]. Delay is a recognised risk factor for nerve function impairment at diagnosis. Identifying underlying causes of delay and finding ways to minimise delay is important in preventing or detecting nerve damage in an early stage. A delay of no more than six months has been proposed as an indicator of good practice in leprosy control [36].

Early and correct assessment of nerve damage is also essential for prevention of disability. If people present with leprosy, hands and feet are tested for loss of feeling (sensory testing) and a number of possible affected muscles are tested for loss of muscle strength (VMT). Sensory testing is preferably done with Semmes-Weinstein monofilaments (MF). Feeling in hands or feet is examined by touching the skin on specific sites with a filament and press until it bends. The bending occurs when a standard force is applied. Filaments with different bending forces are used to assess the severity of sensation loss. Filaments are not always available and require training before use. In practice, a ballpoint pen is often used which is widely available, but less standardised [40-42].

Testing for muscle weakness is done by examining the movement of specific muscles in hands, feet and eyelids. The movements can be graded on a 6-point scale (Medical Research Council grading) or with a simplified grading system (strong, weak, paralysed) [40,43,44]. Recently, new tests, such as nerve conduction and warm detection threshold testing, were found to be promising tests for improving early detection of (subclinical) nerve damage [45].
Nowadays, leprosy control shifts from specialised leprosy clinics towards integration in general health services. General health workers will need to be trained in understanding the basics of leprosy diagnosis and treatment and nerve function testing. Due to their many responsibilities and limited time, rapid and simple, but accurate tests will be needed.

Treatment of nerve damage and reactions

Recent nerve damage (duration less than six months) and severe type 1 reactions can be treated with corticosteroids. These are the drugs of choice but the response to corticosteroid treatment seems to depend on the severity and duration of nerve function impairment before the start of treatment and the duration of treatment [46-48]. The earlier corticosteroids are given after onset of nerve damage, the more likely permanent damage will be prevented [49,50]. In general, about 60% of the people has improved nerve function after corticosteroid treatment [51]. The shortcomings of corticosteroids, including the risk of serious adverse effects, raise the need to find and test alternative drugs and therapies for treating nerve damage. One alternative therapy, which is commonly used in practice, is decompressive surgery. Several studies have shown improvement in nerve function and relief in nerve pain after surgery (e.g. [52-54]). But it is still unclear whether surgery is more beneficial than or adds substantially to corticosteroid treatment. Other therapies, such as azathioprine and ciclosporin, are under investigation or need further examination [51].
Type 2 reaction (ENL) often requires a different treatment than type 1 reactions. The chronic and complex nature of ENL makes it difficult to treat it adequately and safely. Drugs, such as corticosteroids, clofazimine and thalidomide are commonly used, but the optimal treatment remains unclear. Due to serious adverse effects of these drugs, alternative therapies need to be examined [15,55].
If people present with disability due to long-standing nerve function impairment (duration of more than six months), recovery by medical treatment is unlikely. These people may benefit from training in self-care, reconstructive surgery and socio-economic rehabilitation to cope with the disability and to prevent worsening of the disability [31].

Rehabilitation

Over the past 30 years, a comprehensive community development approach, community based rehabilitation (CBR), has been promoted. CBR is defined as ‘a strategy within general community development for the rehabilitation, equalization of opportunities and social inclusion of all people with disabilities. It is implemented through the combined efforts of people with disabilities themselves, their families, organizations and communities, and the relevant governmental and

non-governmental health, education, vocational, social and other services' [56]. Traditionally, leprosy treatment has been carried out by specialised clinics, hospitals and organisations, excluding people affected by leprosy from the general health care system and increasing the risk of stigma. Nowadays, there is a growing trend to integrate leprosy care into general health services and to provide social and economic rehabilitation. New CBR Guidelines are currently developed including a chapter on leprosy. These may contribute to inclusion of people affected by leprosy in general CBR programmes and to enable them "to participate as equal members of the community with equal opportunities and equal rights" [57].

Measures of disability

A commonly used measure is the WHO disability grading for leprosy, which assesses the severity of impairment of eyes, hands and feet. Grade 0 means that neither loss of sensation or visible disability is found in eyes, hands or feet. Grade 1 is given when loss of sensation is present, but no visible disability. Grade 2 means that visible damage or disability is noted. Each hand, foot and eye is graded (six scores). The overall grade for a person is the highest individual grade given [31]. Although this grading is often referred to as WHO disability grades, a more appropriate term would be WHO impairment grades, since the grading addresses only physical impairments [58]. The WHO disability grading can also be used as an indicator of the quality of case detection by monitoring the proportion of people newly detected with WHO grade 2 [27]. To monitor how the physical impairment status changes over time, more detailed grading systems have been developed, such as the EHF (eyes, hands, feet) score [58] or the Impairment Summary Form (ISF) [59].

Since the new ICF definition of disability, the assessment of disability should also take activity limitations and social participation restrictions into account. Two standardised questionnaires for leprosy have been developed, the SALSA scale and Participation scale. They can be used to make comparisons between individuals or groups in different countries, examine changes over time and evaluate interventions. The SALSA scale stands for 'screening of activity limitations and safety awareness'. It was developed especially for people affected by leprosy or diabetes with long-standing peripheral neuropathy. The SALSA scale consists of 20 questions covering mobility, self care, work and dexterity. Each question can be answered as being able to perform the activity or not. If the answer is yes, then the next question is how easy it is to perform the activity. When a negative answer is given, the reason for not being able to perform the activity is asked. A low overall score indicates little difficulty with activities of daily living and higher scores (≥ 25) are associated with increasing levels of activity limitation [60].

The Participation Scale, consisting of 18 items, was developed to measure perceived participation problems in a wide range of life situations as experienced by people affected by leprosy, disability or other stigmatised conditions. In most questions, the respondent is asked to compare his level of participation with that of an actual or hypothetical 'peer'. A peer was defined as 'someone similar to the respondent in all respects (socio-cultural, economic and demographic) except for the disease or disability'. If a person experiences a participation restriction, the next question is

how much of a problem this is to him or her. An overall score of 12 or higher indicates participation problems [61].

III. EVALUATION OF LEPROSY INTERVENTIONS

Measures of effectiveness

Evaluation of leprosy interventions generally aims at identifying and measuring the effects on pre-specified outcomes. Often, these are clinical outcomes, such as improvement in nerve function, change in severity of ENL, reduction in ulcer size, improved grip strength. More recently, quality of life or patient-centred outcome measures have become important indicators of effectiveness, since these take the perspective of individuals into account. Two generic measures which combine both quantity and quality of life are the quality adjusted life years (QALYs) and disability adjusted life years (DALYs). The DALY has been used to measure the burden of leprosy disease, but criticised because the disability weights (0.152 for a leprosy case with disability and 0.000 for a leprosy case without disability) are likely underestimating the actual burden of disease, since they will not adequately capture all the disability resulting from leprosy, such as the major psychosocial and economic impact of leprosy on the lives of individuals, regardless of having disability or not [62]. Leprosy specific quality of life assessment tools are the SALSA scale and the Participation Scale.

An increasingly important outcome measure is cost-effectiveness. Cost-effectiveness analysis is a form of economic evaluation which compares two or more alternative interventions in terms of both costs and effectiveness. Interventions that are less costly and more effective compared to an alternative or existing intervention, give more (health) value for money [63]. This supports the ethical view that "limited resources for health should be allocated to maximise the health benefits for the population served" [64]. Cost-effectiveness analysis also addresses issues such as availability, affordability and sustainability of interventions. These issues often play an important role in decision making in countries with limited resources or in integrated settings.

Evaluating the evidence of effectiveness

Publication of clinical studies in leprosy dates back to the early 1950s when dapsone was introduced for the treatment of leprosy, and immune-suppressant drugs for the management of leprosy reactions were examined. Over the years much clinical and epidemiological research has been conducted in the field of leprosy, but many studies were small-sized and often did not fulfil the rigorous methodological criteria that we have now become accustomed to in clinical research [65]. Systematic reviews or meta-analyses are useful in identifying the best available research evidence and several standard guidelines and checklists are now available to critically appraise reporting and methodology of studies [63,66-70].

IV. RESEARCH QUESTIONS

This thesis aims to define effective approaches and directions for future programmes, research and practice to prevent disability in leprosy. We do so by assessing the effectiveness of interventions for the prevention of permanent disability, such as early detection and treatment of nerve damage and reactions, and of interventions aimed at preventing deterioration of disability (e.g. self-care, footwear, surgery, socio-economic rehabilitation) in leprosy. Prevention of permanent disability refers to preventing the primary consequences of acute nerve damage (sensation loss and muscle paralysis). Deterioration of disability may result from untreated or neglected primary impairment. Examples are ulceration, blindness and deformity. The research questions of this thesis are:

1. How effective are interventions for the prevention of permanent disability in people affected by leprosy?
2. How effective are interventions in preventing deterioration of disability in leprosy?
3. How can programmes aimed at prevention of disability in leprosy be improved?

V. OVERVIEW OF THE STUDY

Several studies have been undertaken to answer the research questions. The first research question is addressed in chapters 3 and 5-7. **Chapter 3** investigates the relationship between detection delay and impairment in two different patient populations. **Chapter 5 and 6** evaluate the effectiveness of corticosteroids and decompressive surgery respectively for treating nerve damage and severe type 1 reactions. **Chapter 7** reviews the benefits of therapies used in the management of type 2 reactions (ENL).
Chapters 8 and 9 refer to the second research question. **Chapter 8** presents the results of a prospective study assessing activity limitation and social participation and the effects of reconstructive surgery on these outcomes in people with hand or foot disability. **Chapter 9** gives a critical overview of cost-effectiveness studies evaluating interventions to prevent disability.
The third research question is partly addressed in chapters 2 and 4 and in the light of the first two research questions. **Chapter 2** explores future trends in the number of people living with disability to give insight in the expected burden of leprosy disability in the coming decades. **Chapter 4** presents the results from a study evaluating three simplified tests to asses for nerve function impairment and discusses the usefulness and feasibility of such tests in integrated health care settings.
The thesis ends with a general discussion (**chapter 10**). This final chapter provides answers to the research questions, and conclusions and recommendations for research and practice.

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CHAPTER 2

Future prevalence of WHO grade 2 impairment in relation to incidence trends in leprosy: an exploration

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SUMMARY

Background: To explore the relationship between leprosy incidence trends and the future prevalence of WHO grade 2 impairment caused by leprosy.

Methods*:* Three scenarios were defined to estimate incidences and prevalences of leprosy impairment beyond 2000, assuming 6%, 12% and 18% annual declines in case detection rate respectively, and 6% impairment among new patients. Case detection data from 1985 to 2000 were used for projecting leprosy incidences up to 2020. To estimate future prevalences of WHO grade 2 impairment, the survival of existing and new impaired individuals was calculated.

Findings: In the 6% scenario, 410 000 new patients will be detected in 2010 and 250 000 in 2020. The number of people living with WHO grade 2 impairment in these years will be 1.3 and 1.1 million, respectively. The 12% scenario predicts that 210 000 new patients will be detected in 2010 and 70 000 in 2020. The grade 2 prevalences will be 1.2 and 0.9 million, respectively. In the 18% scenario, the incidence will be 110 000 in 2010 and 20 000 in 2020, and the grade 2 prevalences will be 1.1 and 0.8 million, respectively.

Interpretation: Declines in numbers of people living with grade 2 impairment lag behind trends in leprosy incidence. The prevalence of people with grade 2 decreases much slower than leprosy incidence and case detection in all three scenarios. This implies that a substantial number of people will live with impairment and will need support, training in self-care and other prevention of disability interventions in the next decades.

INTRODUCTION

Leprosy is a public health problem primarily because it causes impairment and other types of disability. Demands for support and care are driven by the number of people with disability. Information about this number is limited, because the prevalence of disability among leprosy patients has not been monitored systematically. By consequence, only crude estimates are available about the number of people living with disability. In 1995, the World Health Organization (WHO) estimated the number of individuals with grade 2 disability caused by leprosy to be between one and two million [1]. 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" [2].

Although the trends in detection of people with leprosy and related disability appear to be declining, little is known about how much and how fast a decline in incidence and prevalence can be foreseen in the coming decades.

The objective of this study was to gain more insight in the dynamics of the burden of leprosy and demands for support and care in the near future by exploring the relationship between trends in incidence and future prevalence of WHO grade 2 impairment. By using the best available data, trends in expected leprosy impairment prevalences were modelled. Assumptions regarding incidence, case detection and impairment were made for defining different scenarios of numbers of people with WHO grade 2 impairment up to 2020.

METHODS

In this study, three scenarios were provided for the numbers of people living with leprosy and visible impairments up to 2020. These prevalences of leprosy impairment were predicted as follows. First, incidences of impairment were determined by calendar year. Considering available data, three time periods were distinguished in this first step: the years before 1985, the period 1985-2000, and the period 2001-2020. From these incidences, age-specific incidences of impairment were calculated for each calendar year (second step). Thus, each calendar year corresponds to a new cohort of new impaired people of different ages. For each age of each new cohort, survival analysis was carried out to determine what fractions of the cohort would survive until the next year, the second year, the third year and so on until 2020 (third step). The prevalence of leprosy impairment in a calendar year is the sum of the numbers of surviving individuals from all cohorts (fourth step). All calculations were done in Excel spreadsheet. Details on the first three steps are provided below.

Only WHO grade 2 impairment is taken into account, because control programmes as a matter of routine almost exclusively report the percentage of newly detected cases with WHO grade 2. We

define the prevalence of WHO grade 2 impairment as the number of people living with WHO grade 2 impairment worldwide at a given point in time.

Definition of WHO 'disability' grades

The WHO developed a classification for grading leprosy 'disability'. According to the International Classification of Functioning, Disability and Health (ICF), disability includes physical impairments, activity limitations and participation restrictions [3]. Using the ICF definition, the WHO classification for leprosy disability grades impairments rather than disabilities. In this paper we will refer to the WHO leprosy grading as 'WHO impairment grades' or 'WHO impairment status'. The present WHO classification consists of three grades (0-2). Grade 0 means no loss of sensation and no visible deformity, grade 1 is given if loss of sensation exists, but without visible deformity and grade 2 refers to the presence of visible deformity. The grade of impairment is determined for each eye, hand and foot. The maximum grade of any of these body sites is used as an overall indicator of the impairment status of a person with leprosy [2].

Incidence of WHO grade 2 impairment before 1985 (step 1)

Data on worldwide numbers of new leprosy cases and new cases with WHO grade 2 impairment were only available from 1985 onwards. Incidences of WHO grade 2 impairment in the calendar years before 1985 were obtained by backward extrapolation, as follows. First, the case detection rate for 1985 (CDR_{1985}) was calculated by dividing the number of new cases detected in 1985 in the 'top 32' endemic countries by the size of the world population in 1985 (see also next subsection). The resulting estimate for CDR_{1985} is 1.13 per 10 000 population. Of the new cases from these 32 endemic countries in 1985, 9.6% presented with WHO grade 2 impairment [4]. We denote this percentage as $FRAC_{1985}$, and the size of the world population in any given year k as $WPOP_k$. Finally, the incidence of WHO grade 2 impairment in any calendar year k before 1985 was calculated as $FRAC_{1985}$, CDR_{1985}, $WPOP_k$. Estimates for the size of the world population in different years in past and future were obtained from the U.S. Bureau of the Census [5].

Incidence of WHO grade 2 impairment in the period 1985-2000 (step 1)

For each calendar year in the period 1985-1996, numbers of newly detected cases and of newly detected cases presenting with WHO grade 2 impairment were reported consistently for 32 endemic countries [4]. We used the latter figures as estimates for the annual incidences of WHO grade 2 impairment (see also 'Discussion' section). The 32 countries were said to represent 93% of the global leprosy burden in 1997 and 85% of that in 1985.

In 1996, 5.5% of the newly detected cases was reported to have WHO grade 2 impairment [6]. For 1997, 1998 and 1999, only global new case detection figures were reported, and for 2000, both global new case detection and the associated percentage presenting with WHO grade 2 impairment (4%) were reported [7]. The incidences of WHO grade 2 impairment for 1997, 1998, 1999 and 2000 were estimated by multiplying the global case detection figures for these years with the

WHO grade 2 percentages (4% for 2000, interpolation based on 5.5% for 1996 and 4% for 2000 for the years 1997, 1998 and 1999).

The resulting cumulative incidence of WHO grade 2 impairment over the period 1985–2000 was about 680 000 people. The grade 2 incidences for 1985, 1986 to 2000 were respectively: 53 009, 54 203, 51 358, 45 130, 44 104, 45 406, 46 510, 50 288, 50 463, 43 411, 39 966, 29 719, 34 218, 36 708, 30 498, 26 611.

Incidence of WHO grade 2 impairment beyond 2000 (step 1)

Incidences of WHO grade 2 impairment in the calendar years 2001, 2002 to 2020 were predicted as follows. First, the CDRs for these years (CDR_k for year k) were calculated using fixed annual declines that were applied to a baseline CDR of 1.13 per 10 000 population per year. This baseline rate was calculated by dividing all new cases detected globally during 1994-2000 (available from WHO 2002 data [7]) by the aggregated world population size for this period. We used three scenarios for the fixed annual decline: a 6% annual decline, 12% and 18%. The Bangladesh Acute Nerve Damage Study (BANDS) reported that 6% of cases newly detected within the programme had WHO grade 2 impairment [8]. We denote this percentage as $FRAC_{BANDS}$, and the forecasted world population size in any calendar year k beyond 2000 as $WPOP_k$ [5]. Finally, for each of the three annual decline scenarios, we calculated the incidence of WHO grade 2 impairment in year k beyond 2000 as $FRAC_{BANDS}$, CDR_k, $WPOP_k$. The above choices made to calculate the incidence of WHO grade 2 impairment are motivated in the 'Discussion' section.

Age-specific incidence of WHO grade 2 impairment (step 2)

In the earlier section, we described how we calculated the total incidence of WHO grade 2 impairment for any calendar year k. To arrive at the incidence of WHO grade 2 impairment at age a (a=0,...,89) in calendar year k, we subjected the total grade 2 incidence of year k to the age distribution of all newly detected cases who presented with WHO grade 2 impairment within the control programme of the Danish Bangladesh Leprosy Mission in Bangladesh (DBLM, unpublished data over 1986-1990; n=881). We are not aware of published data on age distributions of newly detected leprosy cases presenting with WHO grade 2 in routine control programmes. The mean age of new cases presenting with grade 2 in DBLM was 39 years. The contributions of the 18 age groups 0-4,5-9,...,85-89 to the detection of the 881 newly detected DBLM cases with grade 2 were 0.2%, 0.5%, 4.3%, 5.4%, 9.3%, 11.8%, 13.4%, 11.2%, 11.5%, 6.8%, 8.6%, 5.8%, 5.7%, 2.3%, 2.4%, 0.2%, 0.5%, 0.1%, respectively (we postulated equal shares for the five ages within each 5-year age group).

Survival analysis (step 3)

The maximum age considered by us in this study is 89. We applied age-specific death rates to calculate what fraction of the incident cases of WHO grade 2 impairment of age a in calendar year k, would survive until year $k+1$ (thus having age a+1), until year $k+2$ (thus having age a+2), and so

on until either age 89 or the year 2020. We derived the age-specific death rates from a life table for the general population of Bangladesh for the year 1994 [9]. The life expectancy at birth for Bangladesh was 62 years, which is representative for leprosy endemic countries [10]. According to this life table, the remaining life expectancy at age 39 was 31 years (39 is the mean age at detection of the new DBLM cases presenting with WHO grade 2, see above). We consider the life table from 1994 as a reasonable average for the wide time span that is covered by our survival calculations (e.g. individuals born in 1970 reach age 50 in 2020). For individuals in the age groups 0-4,5-9,...,85-88, the annual death rates were respectively 2.36%, 0.29%, 0.13%, 0.19%, 0.23%, 0.29%, 0.29%, 0.36%, 0.66%, 0.84%, 1.22%, 1.87%, 2.98%, 4.03%, 6.06%, 12.23%, 25%, 50% (the latter two values were chosen by us since the life table did not extend beyond age 80, and the death rate at age 89 was assumed to be 100%).

RESULTS

Incidences of WHO grade 2 impairment

According to our backward analysis, the estimated aggregated incidence of WHO grade 2 impairment up to 1985 was 2.4 million worldwide. During 1985-2000 the aggregated incidence of WHO grade 2 was 680 000.

The incidence of leprosy impairment beyond 2000 was predicted with three different scenarios of annual decline in incidence rate and CDR. Table 1 shows the estimated numbers of new individuals detected with leprosy during 2001-2020, according to the three scenarios. In the 6% scenario, about 250,000 new people will be detected in the year 2020. An annual decline of 12% implies a more than ten-fold reduction in case detection between 2000 and 2020; the case detection has fallen to about 70 000 individuals (72% less than 6% scenario). The 18% scenario predicts that about 20 000 new people will be found, which is 92% less than in the first scenario. Yet even in this scenario, nearly three million people will be detected up to 2010, and almost half a million people between 2010 and 2020.

Table 1. Scenarios for new case detection corresponding to a 6%, 12% and 18% annual decline in the global incidence rate of leprosy beyond the year 2000.

	Number of cases detected		Cumulative number of cases detected in a 10-year time period	
	2010	2020	2001-2010	2011-2020
6% decline scenario	410 000	250 000	5.2 million	3.1 million
12% decline scenario	210 000	70 000	3.8 million	1.2 million
18% decline scenario	110 000	20 000	2.8 million	400 000

Based on the scenarios of leprosy case detection beyond 2000, the incidence of WHO grade 2 impairment was estimated (table 2). In the 6% scenario, the incidence of WHO grade 2 is 15 000 cases in 2020, resulting in an aggregated incidence of grade 2 of 500 000 cases for 2001-2020 as a whole. In the 12% scenario, the annual incidence of grade 2 will have fallen to 4000 people by the year 2020, but the aggregated incidence over 2001-2020 still equals 300 000. In the 18% scenario, the incidence of grade 2 is 1000 cases in 2020, and 200 000 aggregated over 2001-2020.

Table 2. Estimated incidence of 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.

	Number of grade 2 cases		Cumulative number of grade 2 cases in a 10-year time period	
	2010	2020	2001-2010	2011-2020
6% decline scenario	25 000	15 000	310 000	190 000
12% decline scenario	13 000	4000	230 000	70 000
18% decline scenario	6000	1000	170 000	30 000

Table 3. Estimated 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	
	2010	2020
Resulting from cases from before 1985		
Each scenario	460 000	250 000
Resulting from cases detected during 1985-2000		
Each scenario	510 000	380 000
Resulting from cases detected during 2001-2020		
6% decline scenario	300 000	430 000
12% decline scenario	210 000	250 000
18% decline scenario	160 000	160 000
Total prevalence		
6% decline scenario	1.3 million	1.0 million
12% decline scenario	1.2 million	880 000
18% decline scenario	1.1 million	790 000

Prevalences of WHO grade 2 impairment

Table 3 gives estimates of the prevalence of WHO grade 2 impairment in 2010 and 2020. The estimated grade 2 prevalence was 1.3 million in the year 2000, and about one million of these individuals survived up to 2010. This group of people contributes at least 75% to the global WHO grade 2 prevalence in 2010 in all three scenarios. About two-thirds of this group subsequently survives up to 2020 (0.6 million individuals). In this year, the situation per scenario varies more. In the 6% scenario, incident cases from 2001 to 2020 account for about 40% of the global WHO grade 2 prevalence of one million. The contributions are about 28% and 20% for the 12% and 18%

scenario, respectively. In the 18% scenario, the WHO grade 2 prevalence in 2020 is still about 800 000, despite the sharp fall in the incidence of WHO grade 2 impairment to only 1000 in this year.

DISCUSSION

The aim of this study was to gain more insight in the prevalence of leprosy impairment in the foreseeable future. To our knowledge, this is the first time that projections of future impairment are presented. Our predictions are based on the best available leprosy case detection data from the WHO. Our approach was comprehensive, but the outcome should be regarded with some caution. Rather than attempting to provide precise figures, this paper intends to present a systematic way of estimating future trends in leprosy impairment.

Some considerations regarding our analysis are needed. The paper gives an estimation of the total leprosy burden worldwide in the near future. This global leprosy burden was based on data reported from 32 endemic countries. These countries represented 93% of the global leprosy burden in 1997 and 85% of that in 1985 (WHO 1998a). Between 1997 and 2000 the number of newly detected individuals was the sum of five of the six WHO regions. In the sixth region, Europe, no new cases were reported in the previous five years and detection of new individuals was considered negligible.

To obtain leprosy CDRs for the period 2001-2020, we applied fixed annual declines to a baseline CDR. This baseline rate was calculated using the period 1994-2000 as a whole. In the early 1990s case detection figures were relatively constant. In the late 1990s the number of newly detected cases increased substantially, probably due to intensified case-finding efforts and leprosy control activities [11]. Since 2001, the numbers have fallen again. In 2003, the incidence level of the early 1990s was reached and in 2005 the incidence was below this level [12]. It is uncertain how the declining trend will develop in the next decades, but our predictions based on the period 1994-2000 may provide a plausible indicator.

We choose to subject the baseline case detection rate to fixed annual declines of 6%, 12% and 18% beyond 2000, considering an earlier scenario analysis by us [13] and more recent data [12,14]. In this earlier analysis, we estimated that incidence rates of leprosy would decrease with 2-12% per year between 2000 and 2020. Thus, we did not predict declines in the order of 18% per year or more, and the question remains whether the drastic recent declines in case detection observed in several countries reflect genuine declines in leprosy transmission, which will be sustained. The most remarkable decline is seen in India, which had an annual decline of over 30% between 2002 and 2005. This country has dominated the global prevalence and incidence figures for the last decades. In 2002, it contributed for 71% to the total global case detection and in 2005 for 54% [12,14]. It is difficult to explain this drastic reduction in the absence of any systematic nation-wide intervention (e.g. vaccination) aimed at interrupting the transmission of the leprosy bacillus *Myco-*

bacterium leprae [15]. Under the conservative assumption of a decline of 2% per year in incidence rate and CDR, the number of people living with WHO grade 2 impairment remains stable between 2000 and 2020 at 1.3 million individuals. This stability is due to growth of the world population which compensates the 2% decline in incidence and CDR.

For 1985-2000, published data on worldwide detection of new cases presenting with WHO grade 2 impairment were used as direct estimates for the incidence of grade 2. For the other years, grade 2 incidences were obtained by multiplying estimated and predicted CDRs with world population sizes and with the proportion of newly detected cases presenting with grade 2. Here, the assumption is that people with WHO grade 2 impairment will be detected and registered eventually, because of the severe and visible symptoms that usually force people to seek help. This means that for the sake of our calculations, identical annual declines in CDR and incidence rate beyond 2000 can be assumed. Stability in the impairment status of leprosy patients after detection was also assumed, inspired by studies comparing impairment at diagnosis and release from treatment [16]. 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) after release from treatment. The frequency of the reverse – permanent improvement of WHO grade 2 impairment after release from treatment – will probably be lower.

In addition, we assumed that a constant 6% of all new cases detected beyond 2000 will have WHO grade 2. The WHO recently reported that the proportion of newly detected people with grade 2 varies widely across countries, from 1% to 21% [12]. In our opinion, the credibility of proportions in the order of a few percent may be questioned. Our 6% assumption stems from an extensive study conducted within a high-quality control programme with many single lesion leprosy cases [8], and may thus very well be on the conservative side.

Other factors may influence future trends in global prevalence of WHO grade 2 impairment. For instance, the danger exists that decreasing numbers of patients may in the future lead to less awareness of symptoms of leprosy among communities and health workers and to less intensive control efforts. This increases the risk of late presentation and more impairment at the time of detection [17]. The opposite is also possible, because it was assumed that there is no excess mortality in those with WHO grade 2 impairment. Mortality due to leprosy is often not considered important since the disease is rarely a direct cause of death. Only few studies report on leprosy-related mortality. Engers and Morel (2003) estimated that mortality from leprosy worldwide is approximately 4000 individuals per year, which is indeed low considering that all our estimates for WHO grade 2 prevalences are in the order of a million [18]. The WHO estimates for this prevalence in the 1990s were also one to two million [1,2]. From Engers' and Morel's paper, it is unclear how the number of 4000 was calculated and whether and how many deaths resulted directly or indirectly from leprosy. Another study conducted in the Philippines found that the standardised death rate for individuals with lepromatous leprosy was five times higher compared to the general population [19]. Although the study dated from 1954, this result suggests that we may have overestimated prevalences of grade 2 impairment. The sad message would then be that people do needlessly die due to leprosy.

Finally, it is important to keep in mind that trends in prevalence and case detection vary from country to country. Studying changes over time by country or region and underlying mechanisms is recommended to decide on policy and interventions specific to the needs of a country or region. In conclusion, the burden of leprosy consists primarily of impairment and other types of disabilities, which, in turn, have a major impact on the quality of life of the affected individuals. At the same time that the numbers of people with leprosy decrease, there is a danger that attention for the disease and in particular for the needs of people with impairments due to leprosy also becomes less. Our systematically conducted study, based on the best available data, shows that the declining trend in the number of newly detected leprosy cases is substantially faster than the decline in the number of people living with WHO grade 2 impairment. In the near future, we can still expect about one million people affected by leprosy impairment.

For leprosy programme managers these future projections may be very useful in planning leprosy control activities. The most important activity will remain early detection and treatment to prevent impairment and other types of disability. Careful monitoring of the numbers of existing and new impaired individuals enables them to fit interventions to the needs and numbers of people. Awareness of the large number of disabled people due to leprosy in the near future will be needed. Proper health care services, training in self-care and other prevention of disability interventions for these people will continue to be of vital importance in the next decades.

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CHAPTER 3

The relationship between detection delay and impairment in leprosy control: a comparison of patient cohorts from Bangladesh and Ethiopia

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SUMMARY

Background: It is widely acknowledged that longer delays between first symptoms and diagnosis result in more impairment in newly detected leprosy patients. However, it is unclear whether detection delay in relation to impairment can be used as a general or absolute performance indicator of leprosy control programmes. It is unknown whether similar delays always result in similar proportions of impairment. Therefore, the present study examined the quantitative relationship between delay and impairment in two different patient populations.

Methods: Patients from two study cohorts (BANDS and AMFES) who reported voluntarily were included in the analysis. Data on detection delay, WHO impairment status, type of leprosy, age and sex were analysed using descriptive statistics and multivariate logistic regression analysis to identify significant risk factors for impairment and to quantify the relationship between detection delay and impairment status at intake.

Findings: Detection delay was an independent risk factor for impairment at presentation in multivariate analysis. The AMFES cohort reported more impairment at detection than BANDS. In multivariate analysis, this difference was significant among PB patients (51% in AMFES versus 15% in BANDS), but not in MB patients (56% in AMFES versus 45% in BANDS). In fact, for every delay category PB patients from AMFES had much higher proportions of impairment than PB BANDS patients. Impairment rates in MB patients from AMFES were higher in every delay category, but the differences between the two cohorts were much smaller compared to PB patients.

Interpretation: Our analysis confirms earlier findings that with longer delays, the risk of impairment at presentation increases. With the same reported delay, however, the proportion impaired can vary considerably between different patient populations, in particular for PB leprosy. Delay can therefore not simply be used as a general or absolute performance indicator for programme evaluation. Achieving short delays remains important in general, but understanding and addressing the underlying mechanisms of delay specific to a patient population adds substantially to the effectiveness of leprosy control.

INTRODUCTION

Leprosy is a disease especially known and feared because of the nerve function impairment and disabilities that can result. Time plays an important role in the development of leprosy and of nerve damage in particular. Therefore, early detection and treatment of patients is the main focus of leprosy control programmes. The quality of such programmes can be monitored and evaluated with specific indicators. These are tools for measuring the magnitude of the leprosy problem and progress towards achieving the objectives of the programme. Because the leprosy situation differs between countries, programme quality targets should be country-specific and based on recent trends [1]. One indicator of interest in leprosy control is detection delay in relation to the proportion of patients with impairment. Detection delay is defined as the time between noticing the first symptoms and the diagnosis of leprosy. Several studies (e.g. [2-5]) have investigated the relationship between detection delay and the impairment status of leprosy patients at the time of detection. All of these studies found that with longer delays the risk of impairment increases. However, the studies report different impairment rates when the reported delays are the same. For instance, data from Ethiopia showed that 36% of the patients with a delay of 0-1 years presented with impairment, while this proportion was only 12% in Bangladesh [2,3]. Nicholls et al. suggested in an earlier paper that a threshold defining early presentation (e.g. less than six months) could be used as an indicator for good practice in leprosy control [3]. From the data, however, it is unclear whether the relationship between delay and impairment is the same in all situations. For example, is it true that with a delay of less than one year the impairment rate is always 15%? The question thus arises if this relationship is in general valid.

The present study was done to investigate differences in impairment status at the time of detection by comparing two patient populations from different countries. The question posed is whether detection delay in relation to impairment is a generally applicable performance indicator of the quality of leprosy control programmes in terms of reliability and consistency. The overall aim is to obtain a better understanding of the relationship between delay and impairment and the role of early detection in leprosy control.

MATERIALS AND METHODS

Patient populations

For the analysis, two cohorts consisting of newly detected leprosy patients were compared. One cohort was from The Bangladesh Acute Nerve Damage Study (BANDS). This prospective cohort study was supervised by the Danish Bangladesh Leprosy Mission, which runs a well-developed vertical leprosy control programme. The BANDS cohort included 2664 patients newly registered for multi-drug therapy (MDT). Enrolment of patients was from April 1995 to March 1996 [6]. Patient detection was either active or passive. Of the new patients, 43% reported voluntarily (passive

detection) [3]. Full details of the research design and methodology of BANDS can be found in an earlier paper [6].

The other cohort was part of the ALERT MDT Field Evaluation Study (AMFES). The project was carried out in a selected area within the vertical leprosy control programme of ALERT in Central Ethiopia. The study design was a long-term prospective cohort study recruiting new, untreated patients in the period from April 1988 to June 1992 [7]. The AMFES cohort included 592 newly registered patients of whom most reported voluntarily (92%), reflecting the passive nature of case-finding in ALERT's leprosy control programme [2]. An earlier publication describes the design and methods of AMFES in more details [7].

Patient data

For the present comparative analysis, only patients who reported voluntarily (passive case detection) were included. Patients with non-classifiable or missing data on one of the variables of interest were excluded from the analysis. These variables were sex, age, leprosy classification, bacterial index, detection delay and WHO impairment status. The variable age was defined as age at registration in years and divided into five subgroups, following Meima et al. [2]. These age groups were 0-14 years, 15-29 years, 30-44 years, 45-59 years and 60 years and over. Ridley-Jopling classification and skin smear results were available at intake for both cohorts. To enable comparison of the cohorts, these data were used to redefine PB and MB. PB patients were those classified as indeterminate (I), TT, or BT and having a negative skin smear. All BB, BL and LL classified patients and all patients with a positive skin smear were defined as MB [7]. The definition of detection delay as described in the two projects differed. BANDS described detection delay as 'duration of symptoms at registration'. The estimate of the patient was cross-checked against significant data, such as family, local, religious or national events. Delay was recorded in months and years with delays up to one year in months and delays of more than one year primarily in years [3]. In AMFES detection delay was calculated from the mid-year of the calendar year in which the patient had noticed the first symptoms and the registration date [2]. The present study used the delay categories as defined by Meima et al. [2]. These were: up to one year, between one and two years, between two and four years, and more than four years. The BANDS programme recorded delay mostly in rounded years and included one year in the delay category 0-1 year, two years in the delay category 1-2 years et cetera [3]. Impairment status was assessed with the WHO disability grading system (grades 0, 1, 2), in this paper referred to by the more accurate term 'WHO impairment grades' or 'WHO impairment status' [8].

Data analysis

The data analysis was aimed at quantifying the relationship between detection delay and impairment status at intake in two different patient cohorts. For this aim, baseline characteristics of both cohorts were described. Further, logistic regression was conducted to examine whether the

variables sex, age, leprosy classification and detection delay were risk factors for impairment at intake. To test the significance of each of these risk factors, odds ratios were calculated with 95% confidence intervals. A multivariate logistic regression model was used to test the significance of a risk factor independent of the other risk factors in the model. The multivariate analysis was carried out using a model with all risk factors included simultaneously. For comparison between the two cohorts, these regression analyses were done for both cohorts separately and for the combined cohort with respect to leprosy type (PB or MB). The statistical programme SPSS was used for the analysis.

RESULTS

Patient characteristics

To enable comparison, only patients who reported voluntarily (passive case detection) were included. In the BANDS cohort, 1133 out of 2664 patients (43%) reported voluntarily, while the AMFES cohort had 538 out of 586 self-reported patients (91%). From these 1671 passively detected patients, 77 patients were excluded from the analysis. These were patients without data on bacterial index (*n*=17) or delay (*n*=5). Neural leprosy (NL) patients were not classifiable as either PB or MB patients and therefore also excluded from the analysis (*n*=55). Thus a total of 1594 newly registered patients from AMFES and BANDS were available for analysis. Table 1 shows characteristics of the patients at intake according to cohort.

Sex and age distribution were comparable between the two projects. Differences were observed in leprosy type, impairment status at intake and detection delay. The distribution of PB and MB patients was almost equal (48% versus 52%) in the AMFES cohort, while the BANDS cohort had 90% PB patients and only 10% MB patients. Impairment at intake was three times higher in the AMFES cohort compared with the BANDS cohort (54% versus 18%). With respect to delay, patients in the BANDS cohort presented earlier than patients from the AMFES cohort (57% versus 26% delay up to one year).

Analysis of risk factors for presentation with impairment

To examine the differences in impairment at intake, regression analysis was performed for the combined cohort and for each cohort alone. Outcomes from univariate analysis were almost similar to the multivariate ones. Therefore, only the multivariate results are given in table 2.

Table 1. Characteristics of new patients at intake by cohort.

	AMFES (*n*=517)		BANDS (*n*=1077)	
Characteristic	no. cases	% of all cases	no. cases	% of all cases
Sex				
Male	325	63	672	62
Female	192	37	405	38
Age in years				
0-14	72	14	182	17
15-29	214	41	313	29
30-44	110	21	320	30
45-59	83	16	184	17
≥ 60	38	7	78	7
Type				
PB	248	48	974	90
MB	269	52	103	10
Impairment status				
Grade 0	240	46	882	82
Grade 1	158	31	115	11
Grade 2	119	23	80	7
Delay in years				
0-1	136	26	613	57
1-2	161	31	218	20
2-4	144	28	121	11
≥ 4	76	15	125	12

Table 2a shows the results for the combined cohort. From this table, it can be seen that a significantly higher proportion of impaired PB patients was found in Ethiopia than in Bangladesh (51% versus 15%), but this was not the case for MB patients (56% versus 45%). Differences in impairment rates between the two cohorts were mainly observed in PB patients. Sex was not found to be an independent risk factor for presenting with impairment. Only among PB patients, females had a significantly lower risk of impairment than males, but the difference was not very strong (p=0.03). In both cohorts, higher age and longer delays were strongly associated with an increased risk of impairment at intake.

Table 2. Multivariate logistic regression odds ratios and 95% confidence intervals of risk factors for impairment at intake based on PB AMFES-BANDS cohort and MB AMFES-BANDS cohort.

Risk factor	No. impaired (% of cases within subgroup)	Multivariate odds ratio (95% confidence interval)	No. impaired (% of cases within subgroup)	Multivariate odds ratio (95% confidence interval)
a) AMFES+BANDS	PB (*n*=1222)		MB (*n*=372)	
Sex				
Male	182/738 (25%)	baseline[1]	140/259 (54%)	baseline[1]
Female	94/484 (19%)	0.70 (0.51-0.96)[2]	56/113 (50%)	0.87 (0.53-1.42)
Age in years				
0-14	22/214 (10%)	0.60 (0.34-1.05)	8/40 (20%)	0.29 (0.12-0.70) [2]
15-29	66/383 (17%)	baseline[1]	68/144 (47%)	baseline[1]
30-44	77/324 (24%)	2.12 (1.40-3.22)[2]	66/106 (62%)	1.86 (1.08-3.22) [2]
45-59	74/207 (36%)	3.44 (2.23-5.33) [2]	37/60 (62%)	1.76 (0.92-3.38)
≥ 60	37/94 (39%)	3.52 (2.04-6.07) [2]	17/22 (77%)	3.62 (1.20-10.90) [2]
Delay in years				
0-1	92/636 (15%)	baseline[1]	39/113 (35%)	baseline[1]
1-2	68/273 (25%)	1.41 (0.95-2.07)	55/106 (52%)	1.98 (1.10-3.56) [2]
2-4	65/165 (39%)	2.35 (1.53-3.60) [2]	60/100 (60%)	2.70 (1.47-4.97) [2]
≥ 4	51/148 (35%)	2.38 (1.53-3.69) [2]	42/53 (79%)	6.23 (2.76-14.1) [2]
Cohort				
BANDS	149/974 (15%)	baseline[1]	46/103 (45%)	baseline[1]
AMFES	127/248 (51%)	6.73 (4.76-9.51) [2]	150/269 (56%)	1.25 (0.73-2.14)
b) AMFES	PB (*n*=248)		MB (*n*=269)	
Sex				
Male	79/146 (54%)	baseline[1]	104/179 (58%)	baseline[1]
Female	48/102 (47%)	0.95 (0.52-1.71)	46/90 (51%)	0.82 (0.46-1.44)
Age in years				
0-14	13/46 (28%)	0.58 (0.25-1.30)	6/26 (23%)	0.30 (0.11-0.85) [2]
15-29	37/96 (39%)	baseline[1]	60/118 (51%)	baseline[1]
30-44	28/42 (67%)	2.40 (1.06-5.46) [2]	44/68 (65%)	1.46 (0.76-2.81)
45-59	31/41 (76%)	5.25 (2.23-12.39)[2]	28/42 (67%)	1.57 (0.72-3.42)
≥ 60	18/23 (78%)	5.73 (1.84-17.85) [2]	12/15 (80%)	4.14 (1.02-16.8) [2]
Delay in years				
0-1	30/78 (38%)	baseline[1]	16/58 (28%)	baseline[1]
1-2	31/79 (39%)	1.22 (0.60-2.48)	45/82 (55%)	3.05 (1.43-6.50) [2]
2-4	41/58 (71%)	3.90 (1.76-8.65) [2]	54/86 (63%)	4.24 (1.98-9.05) [2]
≥ 4	25/33 (76%)	6.13 (2.26-16.60) [2]	35/43 (81%)	10.2 (3.80-27.7) [2]
c) BANDS	PB (*n*=974)		MB (*n*=103)	
Sex				
Male	103/592 (17%)	baseline[1]	36/80 (45%)	baseline[1]
Female	46/382 (12%)	0.63 (0.43-0.92) [2]	10/23 (44%)	1.19 (0.42-3.35)
Age in years				
0-14	9/168 (5%)	0.55 (0.25-1.20)	2/14 (14%)	0.37 (0.06-2.11)
15-29	29/287 (10%)	baseline[1]	8/26 (31%)	baseline[1]
30-44	49/282 (17%)	1.90 (1.16-3.13) [2]	22/38 (58%)	3.18 (1.06-9.53) [2]
45-59	43/166 (26%)	2.98 (1.76-5.05) [2]	9/18 (50%)	2.26 (0.63-8.18)
≥ 60	19/71 (27%)	2.84 (1.47-5.50) [2]	5/7 (71%)	4.39 (0.62-31.3)
Delay in years				
0-1	62/558 (11%)	baseline[1]	23/55 (42%)	baseline[1]
1-2	37/194 (19%)	1.69 (1.07-2.67) [2]	10/24 (42%)	1.05 (0.37-3.05)
2-4	24/107 (22%)	1.92 (1.12-3.29) [2]	6/14 (43%)	1.28 (0.36-4.61)
≥ 4	26/115 (23%)	1.83 (1.08-3.10) [2]	7/10 (70%)	2.75 (0.56-13.6)

[1] baseline or reference subcategory [2] significant

When examining the cohorts separately, some differences were observed. Sex was only significant in the PB BANDS cohort (p=0.02). Overall, age was an independent risk factor in both cohorts, but less significant for MB patients. Among PB patients, the influence of age was more marked in the AMFES compared with the BANDS cohort. Increasing delays were significantly associated with impairment, except among MB BANDS cohort patients. The effects of delay were much stronger in the PB AMFES cohort compared to the PB BANDS cohort. Not only did PB patients in the AMFES cohort have more impairment in each delay category, the increase in impairment rate with longer delays was much larger. The relationship between impairment at intake and delay are illustrated in figure 1.

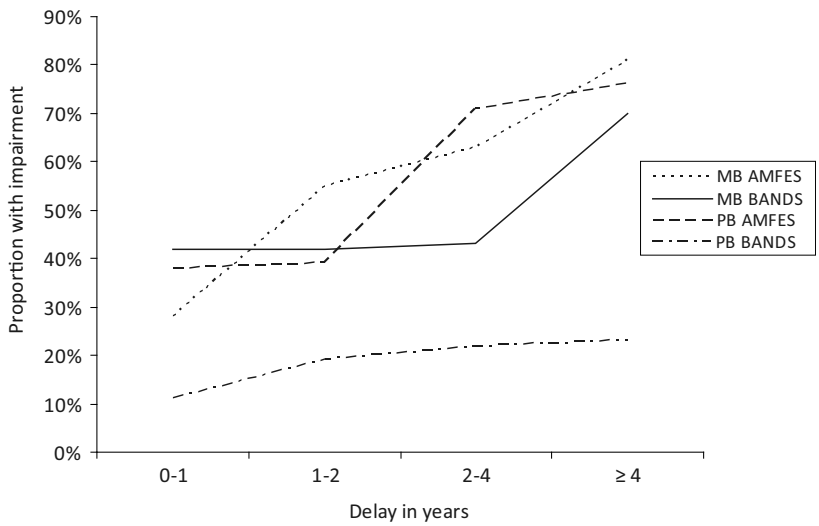

Figure 1. Relationship between impairment at intake and delay by leprosy type and cohort.

The two MB lines, one for each cohort, have different shapes. The BANDS curve starts with a higher proportion of impairment than that for AMFES, but remains at a constant level for delay up to four years. In contrast, the AMFES cohort shows a gradually increasing line, reflecting higher impairment rates with longer delays. When delays become longer than four years, the BANDS cohort shows a rapid increase in the proportion impaired. At this point, the impairment rates are very comparable, with the AMFES cohort having 81% impairment and the BANDS cohort reporting 70% impairment. The PB curves of both cohorts show also different patterns. The AMFES curve starts with a higher proportion of impairment and suddenly becomes steeper at a delay of more than two years. For the BANDS cohort, the line starts with a relatively low impairment level and remains quite flat with only a slight increase when delays become longer. When delays are four years or more, the proportion with impairment is more than three times higher in the AMFES than

in BANDS cohort (76% versus 23%). The differences in impairment rate are more pronounced in the PB group, as can be observed from the larger distance between the two PB curves compared to the MB curves.

Analysis of possible confounders

The relationship between delay and impairment was studied in more detail by checking for confounding variables. Sex and age had almost similar distributions in both cohorts. Although the distribution of PB and MB patients was different in AMFES and BANDS cohorts, the proportions of patients according to the Ridley-Jopling classification were nearly the same in the two cohorts. The case-finding methods differed in both cohorts. In the AMFES cohort, almost all patients reported voluntarily (91%), while in the BANDS cohort only 43% of all patients were detected passively. From the BANDS data, it could be seen that in both the PB and MB groups, passively detected patients had more impairment and MB patients were more impaired than PB patients. However, the differences with actively found patients, also when taking delay into account, were not large.

The Ridley-Jopling classification does not take into account the number of skin lesions, so we examined this separately. Data on skin lesions were only available for the BANDS cohort. The results are shown in table 3. Of the 969 PB patients, 86% had five or less skin lesions and 14% more than five skin lesions. Impairment rates increased with higher numbers of skin lesions. While patients with less than five skin lesions had low impairment rates, for patients with more than five skin lesions the proportion with impairment was nearly as high as for PB AMFES patients (41% versus 51%). The impairment rates of the last two groups were also comparable with respect to the delay categories.

Table 3. Frequency distribution of impairment at intake in 969 passively detected PB patients from BANDS by delay and skin lesions[1]

Delay in years	1 lesion (52%)	2-5 lesions (35%)	> 5 lesions (14%)
	No. impaired (% of cases within subgroup)	No. impaired (% of cases within subgroup)	No. impaired (% of cases within subgroup)
0-1	18/294 (6)	21/197 (11)	23/66 (35)
1-2	10/86 (12)	12/72 (17)	14/35 (40)
2-4	6/54 (11)	7/33 (21)	9/18 (50)
≥ 4	10/66 (15)	7/35 (20)	8/13 (62)
Total	44/500 (9)	47/337 (14)	54/132 (41)

[1] From the 974 passively detected PB patients there were five patients with missing data on skin lesions. Four of them had impairment. These five patients were excluded from the analysis.

DISCUSSION

Detection delay is often seen as an important risk factor for the development of impairment. Therefore, many leprosy control programmes give high priority to early detection of leprosy patients. A tool that can predict the proportion with impairment for different delays in all situations would thus be very helpful. The objective of this study was to examine the quantitative relationship between detection delay and impairment in two different patient populations. The question to be answered was whether detection delay in relation to impairment is a generally applicable performance indicator of leprosy control programmes. The main finding was the higher impairment rates in AMFES compared with the BANDS cohort, while the duration of the delay was the same. This suggests that the relationship between delay and impairment is not consistent across populations. For example, of all PB patients presenting with a delay of more than four years, 76% were impaired in the AMFES cohort and only 23% in BANDS. Similar to other studies, we found that with longer delays the risk of impairment increases. The differences were most striking among PB patients.

There were some difficulties in making a good comparison between the two populations. Firstly, it was necessary to redefine the leprosy classification, because different definitions were used in the studies. If this was not done, 8% of the patients classified as MB in BANDS would have been labelled PB in AMFES. Although this is a small proportion, differences in definition may have a confounding effect on the size and direction of the relationship between delay and impairment in the different defined groups. Secondly, since 1998 the World Health Organization (WHO) recommends that PB and MB classification is based on skin lesion count only; patients with one to five lesions are PB and patients with six or more lesions are MB [9]. Neither of the studies in this analysis used these current WHO criteria. Skin lesion count data were only available for BANDS. The BANDS data show that 132 out of the 969 passively detected PB patients had more than five lesions (14%). The impairment rates of these PB patients were very comparable to the ones found in AMFES PB patients.

Several factors may have a confounding effect when comparing detection delay in different populations. Various studies describe factors related to delay in presentation and start of treatment. The most important reasons found for delay are inadequate knowledge and awareness of the disease and its early symptoms, more belief in traditional medicine as first action, misdiagnoses and stigma among staff and poor accessibility to health services [10-15].

In the present study some confounding factors may have played a role in comparing the data. First, the assessment of detection delay depended mainly on the recall of the patients themselves. With longer duration of the disease, inaccuracy of recall will be more likely. Differences in recall form an important source of bias. Also, the reported delay might have depended on knowledge and awareness of symptoms. It might be that nerve damage rather than skin patches are regarded

as first sign of leprosy due to inadequate knowledge. This may have led to underreporting of the actual delay, especially in Ethiopia, where leprosy control is less well-developed. In addition, the two studies used different methods to define the duration of detection delay. Therefore, the data were transformed for comparison which also can cause bias.

Another difficulty in the comparison were differences between the leprosy control programmes. Two important aspects here are case finding methods and the coverage of leprosy services. With regard to case finding, in the AMFES programme the vast majority of patients reported voluntarily (passive case detection), while in the BANDS programme, 43% reported voluntarily. More than half of the patients were found actively in BANDS (57%). It is possible that patients were found in BANDS who would not have been detected if there had been no active case finding. The active nature of the BANDS control programme might also have led to more awareness among the general population of signs and symptoms of leprosy and thus to earlier presentation of individuals with the disease, in particular of PB patients who have a limited number of skin lesions and no nerve damage. Also, the coverage of leprosy services in terms of availability and accessibility is much better in the BANDS districts than in the AMFES area, making it easier for BANDS patients to visit a clinic [6,7,15]. The difference in degree of delay between AMFES and BANDS may thus in part be caused by the difference in leprosy control, with the AMFES programme functioning at a more basic level than the BANDS programme. Finally, the differences in impairment and delay may also reflect biological variety, although no evidence is available to confirm this.

We did not include patients with neural leprosy (NL) in the analysis, because these patients were not classifiable as either PB or MB patients. In AMFES there were 3 NL patients, all with impairment. The BANDS cohort had 52 NL patients, 35 of whom had impairment (67%). Because of the high impairment rates in this group of leprosy patients, examining this group in more detail would be indicated. Due to the explorative nature of this study, we only compared two patient populations. To validate and explain further the results found in this study, analysis of more patient cohorts would be needed.

From this study it is clear that the relationship between delay and impairment must be seen in the light of the context (e.g. patient population, quality of the leprosy programme, social and cultural attitudes and beliefs). Also, the need for uniform definitions and classification becomes visible when doing comparative analysis.

We conclude that our data support the hypothesis that delay is a useful, but relative indicator. Shorter delays are in general indicative of lower impairment rates. However, with similar reported delays these rates can vary greatly between different patient populations, especially among PB patients. Delay can therefore not simply be used as a general or absolute performance indicator for programme evaluation. Understanding why certain patients or populations delay more than other patients or populations should be just as important as achieving short delays in prevention of disability (POD) programmes.

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CHAPTER 4

Evaluation of simplified tests for the diagnosis of nerve function impairment in leprosy: the Sensory Motor Screening (SMS) study

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SUMMARY

Background: Rapid and simple tests for diagnosing nerve function impairment (NFI) in leprosy are required in integrated settings. We examined whether simplified tests performed by newly trained general health workers (GHWs) have comparable diagnostic accuracy to the reference test conducted by experienced physiotherapists.

Methods: This multi-centre study from India and Bangladesh evaluated three simplified tests named: ILEP Learning Guide Two (M2), Indian dance (M3) and a questionnaire (M4) in 408 people affected by leprosy. Sensitivity (Se) and specificity (Sp) of the three tests were calculated using the full assessment (M1) as reference. Se and Sp were calculated at both whole body and individual nerve levels: whether any NFI and if single NFI (voluntary muscle testing of lid gap, eye closure, little finger out, thumb up and foot up, sensory testing of hands and of feet) was present.

Findings: M2 had 83% Se and 69% Sp, M3 had 76% Se and 84% Sp and M4 had 85% Se and 46% Sp in diagnosing any NFI. At the level of single NFI, M2 was most or similarly accurate in diagnosing single NFIs with highest prevalence (ST feet, ST hands, little finger out, thumb up), compared to M3 and M4.

Interpretation: ILEP Learning Guide Two (M2) and Indian dance (M3) were found to be the most accurate simplified tests for diagnosing the presence of NFI compared to the reference. M2 was the most useful test, because of greatest accuracy for most of the common types of NFI and inclusion of sensory testing of the hands. M2 is considered to be a useful tool in the hands of GHWs with time constraints in integrated settings.

INTRODUCTION

In leprosy-endemic countries such as India, leprosy control is increasingly being integrated into the general health services. General health workers (GHWs) need to understand the basics of leprosy diagnosis and treatment to address the specific needs of people affected by leprosy and to prevent disability [1,2]. Due to their many responsibilities and limited time, leprosy training for GHWs needs to be simple, easy to remember and effective. A key element of such training is how to assess for nerve function impairment (NFI).

Established methods for nerve function assessment in leprosy are sensory testing (ST) and voluntary muscle testing (VMT). Graded monofilaments and ballpoint pen are commonly used for ST. The ballpoint pen is considered less standardised than monofilaments, but is widely available [3-5]. For VMT, the modified MRC scale (0-5) is a reliable method for grading muscle strength [5-7]. The accurate use of graded monofilaments and the modified MRC scale requires training and acquired skill. Several studies indicate that skill and experience levels affect reliability of testing [4,5,7,8]. Simplified tests will be more feasible for GHWs to learn and use in a reliable way. They should be sensitive enough to correctly diagnose NFI (low number of false-negatives), but also specific enough not to over-diagnose NFI (low number of false-positives).

Several simplified tests have been developed and used in the field. One is the ILEP Learning Guide Two, which was written for health workers who may have to manage the early complications of leprosy [9]. Another test was proposed by Fritschi using a posture derived from an Indian dance [10]. A third simplified test, a screening questionnaire, was derived from a questionnaire developed at the International Workshop on Measuring Disablement in Karigiri, India in 2000. The questionnaire has been introduced to GHWs in a project aimed at prevention of impairment and disability (POID in six States of India). It is still used, but has been modified, including some added questions on reaction and neuritis. We do not know of any published studies describing or comparing the performance of these three tests in terms of sensitivity and specificity.

The purpose of the present study was to investigate the diagnostic accuracy of these three simplified tests when carried out by newly trained GHWs as compared to a full assessment (reference test) conducted by experienced physiotherapy staff. The main research question was: which simplified test is most useful in the hands of GHWs in terms of sensitivity and specificity?

MATERIALS AND METHODS

General health workers (GHWs)

Seven leprosy referral centres in India (Karigiri, Faizabad, Naini, Muzaffarpur, Purulia, Kolkata, Salur) and one in Bangladesh (Nilphamari) participated in the study.

In each centre, GHWs were recruited who had a general health background, but no previous experience in leprosy. The 30 volunteer testers in this study came from a variety of health backgrounds and included nursing students, physiotherapy students, prosthetic & orthotic engineering students, homeopathic doctors, pharmacists, staff nurses, occupational therapists and government health assistants. All recruits received 2-days training in leprosy, NFI and the use of a simplified test. Each GHW was trained to use only one simplified test. At each centre two simplified tests were taught, with 1-3 GHWs trained in each test.

Patients

For this study, patients eligible for inclusion were leprosy patients aged between 15 and 65 years and able to understand and follow instructions. In each centre, patients who came to the hospital outpatient department for treatment received routine assessment by a physiotherapy staff member who had 4-35 years (mean: 15) working experience in leprosy, using the reference test. If patients were found to be eligible, they were informed about the study and asked to participate. Those who gave informed consent were also assessed the same day by the newly trained GHWs using one or two of the simplified tests. Each centre recruited patients until they had included at least 50 patients in the study. Only in Bangladesh was this target not achieved. The total data collection covering the eight centres lasted for a nine-month period in 2004 and resulted in the inclusion of 408 patients into the study.

Testing procedure

The GHWs were blinded to the participants' records and to the results of the full assessment. They received only a referral slip with the name and identification number of the participating patient. Assessments were done in a suitable space away from distractions by other staff or patients. Different testers in the same centre worked in different locations to ensure blinding to other assessment results. The order in which testers assessed patients was randomised.

Each assessor returned the completed forms to the study coordinator who checked that each form was completed, but did not evaluate the results. Results were then entered into a database by data clerks in a central location.

METHODS

Method 1: reference test (M1)

The full assessment used to diagnose NFI consists of sensory and motor nerve function testing. Sensory testing was done using a 2 g monofilament for the hand and a 10 g monofilament for the feet. On each hand, four points on the ulnar nerve and six points on the median nerve were tested. On each foot, ten points in the area of the posterior tibial nerve were tested [11]. Sensory NFI was defined as loss of feeling in two or more points on any nerve of the hand or foot. Muscle strength was tested with the modified Medical Research Council (MRC) scale (0-5). Muscles innervated by the facial, ulnar, median, radial, and lateral popliteal nerves were assessed by asking the participant to perform five movements: eye closure, little finger abduction, thumb abduction, wrist extension, and ankle dorsiflexion [12]. Motor NFI was defined as a score of less than four for any movement. Results of nerve palpation and any other eye defects present were also recorded.

Method 2: ILEP Learning Guide Two (M2)

The simplified assessment test proposed in the ILEP Learning Guide Two [9] tests four points for sensation on each hand (two ulnar nerve and two median nerve sites) and foot (posterior tibial nerve) with a ball-point pen. Four movements (eye closure, little finger out, thumb up and foot up) test facial, ulnar, median and lateral popliteal motor nerve function respectively, using a grading system of three categories (strong, weak, paralysed). Sensory NFI is defined as loss of feeling in one or more points for any hand or foot, while motor NFI is defined as scoring less than 'strong' for any muscle. M2 also examines for nerve tenderness and asks the participant about any recent vision loss, any sensation loss, any pain or burning/tingling sensation and any red or inflamed skin patches.

Method 3: Indian dance (M3)

Another simplified test to assess for NFI proposed by Fritschi is asking participants to assume a posture derived from an Indian dance [10]. It primarily tests motor nerve function by asking patients to perform four movements; eye closure, opposition of the little finger and thumb whilst maintaining interphalangeal joint extension, wrist extension, and ankle dorsiflexion. Sensory nerve function is tested by stroking the lateral sides of both feet with a finger. NFI is defined as not being able to perform any of the movements or not feeling the stroking on either side.

Method 4: screening questionnaire (M4)

A third simplified test, using a screening questionnaire, has been introduced to some GHWs in India. In this test motor (facial, ulnar, median and lateral popliteal) and sensory (ulnar, median and posterior tibial) nerve function are simply tested by observing and questioning the patient about signs and symptoms of nerve function loss. The questionnaire consists of five observations and

eight questions. NFI is defined as answering negatively to any of the observations or questions. An overview of NFI definitions and tests can be found in the Annex (Tables I and II and Figures I-IV).

Data analysis

The results were analysed by investigators who were not involved in the assessments. The results of each simplified test (M2, 3 or 4) were compared with the results of M1 obtained in the same subjects. For the comparisons, variables were dichotomised (yes/no NFI) and new variables were computed for the eyes, hands and feet based on the eye, hand or foot with the lowest score. The following variables were included in the analysis: sensory testing of the hands (ST hands), sensory testing of the feet (ST feet), little finger abduction (finger out), thumb abduction (thumb up), wrist extension (wrist up), ankle dorsiflexion (foot up), strong eye closure (eye closure) and presence of lid gap (lid gap).

For each comparison, sensitivity (Se) and specificity (Sp) and their two-sided 95% confidence intervals (CIs) were calculated as measures of diagnostic accuracy. Sensitivity is the proportion of people with NFI according to M1 and being diagnosed by the simplified test as having NFI and Sp is the proportion of people not having NFI according to M1 and being diagnosed by the simplified test as not having NFI. Prevalence (Pr) was defined as the number of people with NFI according to M1, as a proportion of the total number of people. For all our analyses, we used the statistical software package SPSS (version 15.0).

RESULTS

Characteristics of study population

A total of 408 participants were fully assessed for nerve function impairment (NFI) with the reference test (M1). Of this number, 287 (70%) were examined with M2, 238 (58%) with M3 and 280 (69%) with M4. There were 337 males (83%) and 71 females (17%) included. The mean age was 36 years. Most participants were currently receiving MDT treatment (62%). About half of the participants had NFI according to M1. The centre in Bangladesh had the fewest number of participants compared to the other centres. Results are shown in Table 1.

Overall testing

The overall performance of the tests was compared to the reference (M1). It is a measure of how accurate a test is in diagnosing any NFI. For example, if M1 diagnosed sensory NFI of the hands and M2 diagnosed motor NFI of foot up on the same patient, then the overall result was that M1 and M2 agreed on the presence of NFI in this patient. This result tells us whether patients would be referred or treated, but does not tell us whether M2 referred or treated for the same reason as M1. M2 and M4 agreed with M1 more often on the presence of any NFI than on the absence of any

NFI. M3 was better in the opposite, with relatively less false positives, but more false negatives. M2 misdiagnosed 23% of all patients. This is the error rate (ER) which is the proportion of patients who are either incorrectly classified as not having any NFI (false negatives) or as incorrectly having NFI (false positives). M3 and M4 had an ER of respectively 21% and 32%. Results are shown in Table 2.

Table 1. Characteristics of the study population.

Characteristic	Total (*n*=408)	M1 vs. M2 (*n*=287)	M1 vs. M3 (*n*=238)	M1 vs. M4 (*n*=280)
Sex in no. (%):				
Male	337 (83)	245 (85)	195 (82)	224 (80)
Female	71 (17)	42 (15)	43 (18)	56 (20)
Age in years:				
Mean ± SD	36 ± 14	36 ± 14	37 ± 14	36 ± 14
Range	15-65	15-65	15-65	15-65
Treatment status in no (%):				
On MDT treatment	253 (62)	152 (53)	168 (71)	179 (64)
Released from MDT treatment	155 (38)	135 (47)	70 (29)	101 (36)
*NFI present in no (%)**				
Yes	236 (58)	166 (58)	144 (61)	157 (56)
No	172 (42)	121 (42)	94 (39)	123 (44)
Centre in no.(%):				
Karigiri	55 (14)	53 (18)	55 (23)	-
Faizabad	54 (13)	-	54 (23)	54 (19)
Naini	50 (12)	50 (17)	-	50 (18)
Muzaffarpur	60 (15)	60 (21)	60 (25)	-
Purulia	59 (15)	-	59 (25)	59 (21)
Kolkata	57 (14)	57 (20)	-	57 (20)
Salur	60 (15)	58 (20)	-	60 (21)
Nilphamari	13 (3)	9 (3)	10 (4)	-

* according to M1

Table 2. Comparison of the three simplified test methods (M2, 3, 4) with the reference (M1): overall testing

M1 vs.	True positives	False negatives	False positives	True negatives	Total	Sensitivity (95% CI) %	Specificity (95% CI) %	Prevalence %
M2	138	28	37	84	287	83 (77-88)	69 (61-77)	58
M3	109	35	15	79	238	76 (68-82)	84 (75-90)	61
M4	134	23	67	56	280	85 (79-90)	46 (37-54)	56

M1 vs. M2: lid gap, eye closure, finger out, thumb up, foot up, ST hands, ST feet
M1 vs. M3: lid gap, finger out, thumb up, wrist up, foot up, ST feet
M1 vs. M4: lid gap, finger out, thumb up, foot up, ST hands, ST feet

Motor testing

The performance of the tests on single voluntary muscle testing (VMT) components was compared to the reference to indicate how accurate a test was in diagnosing a specific NFI. For example, if both M1 and M2 diagnosed motor NFI of thumb up on the same patient, then the result was that M1 and M2 agreed on the presence of NFI in this patient.

Sensitivity of eye closure testing was less than 50%, meaning that people with NFI were relatively often missed, although eye NFI was fairly infrequent (*Pr* < 5%). Simplified finger out, thumb up and foot up testing were more accurate. The prevalence of foot up NFI was not very high (≤ 5%), and sensitivity of this test was relatively low in M2. The most common types of motor NFI were finger out and thumb up NFI, for which sensitivity was relatively low in M3. Specificity was low for thumb up testing in M4. M2 was most accurate in diagnosing these frequently occurring types of NFI. Strong eye closure and wrist up testing were only done in M2 and M3 respectively. Results are shown in Table 3.

Table 3. Comparison of the three simplified test methods (M2, 3, 4) with the reference (M1): voluntary muscle testing (VMT).

M1 vs.	True positives	False negatives	False positives	True negatives	Total	Sensitivity (95%CI) %	Specificity (95%CI) %	Prevalence %
VMT:								
Lidgap[1]								
M2	3	6	43	233	285*	33 (11-67)	84 (80-88)	3
M3	3	1	6	227	237*	75 (24-97)	97 (94-99)	2
M4	2	7	3	267	279*	22 (6-58)	99 (97-100)	3
Eyeclosure								
M2	5	5	21	254	285*	50 (23-78)	92 (89-95)	4
Fingerout								
M2	45	13	41	188	287	78 (65-87)	82 (77-87)	20
M3	26	25	17	170	238	51 (38-64)	91 (86-94)	21
M4	35	13	32	200	280	73 (59-84)	86 (81-90)	17
Thumbup								
M2	19	6	17	245	287	76 (56-89)	94 (90-96)	9
M3	6	12	13	207	238	33 (16-57)	94 (90-97)	8
M4	12	3	112	153	280	80 (53-93)	58 (52-64)	5
Footup[1]								
M2	8	7	11	258	284*	53 (29-76)	96 (93-98)	5
M3	7	1	13	216	237*	88 (46-98)	94 (91-97)	3
M4	9	3	8	260	280	75 (45-92)	97 (94-99)	4

[1] M2 had less than ten true positives for lid gap, M3 for VMT wrist up, foot up and lid gap and M4 for lid gap
* missing values

Sensory testing

Sensory NFI was more often diagnosed by M1 than motor NFI. When comparing single sensory testing (ST) components to the reference, M2 and M3 had lower sensitivity but better specificity (more false negatives) compared to M4 which was less specific and more sensitive (more false positives). M3 did not test for sensory NFI of the hands. Results are shown in Table 4.

Table 4. Comparison of the three simplified test methods (M2, 3, 4) with the reference (M1): sensory testing (ST)

M1 vs.	True positives	False negatives	False positives	True negatives	Total	Sensitivity (95%CI) %	Specificity (95%CI) %	Prevalence %
ST:								
Hands								
M2	56	22	7	202	287	72 (61-81)	97 (93-98)	27
M4	54	22	70	134	280	71 (60-80)	66 (59-72)	27
Feet								
M2	89	46	11	141	287	66 (58-73)	93 (87-96)	47
M3	80	33	9	116	238	71 (62-78)	93 (87-96)	47
M4	96	28	44	112	280	77 (69-84)	72 (64-78)	44

Relationship between number of NFI and sensitivity

The chance of diagnosing that a patient had any NFI according to both the test and the reference (sensitivity) increased if this patient had multiple NFI. Figure 1 shows this relationship. Once a patient had four or more types of NFI, all test methods had 100% Se.

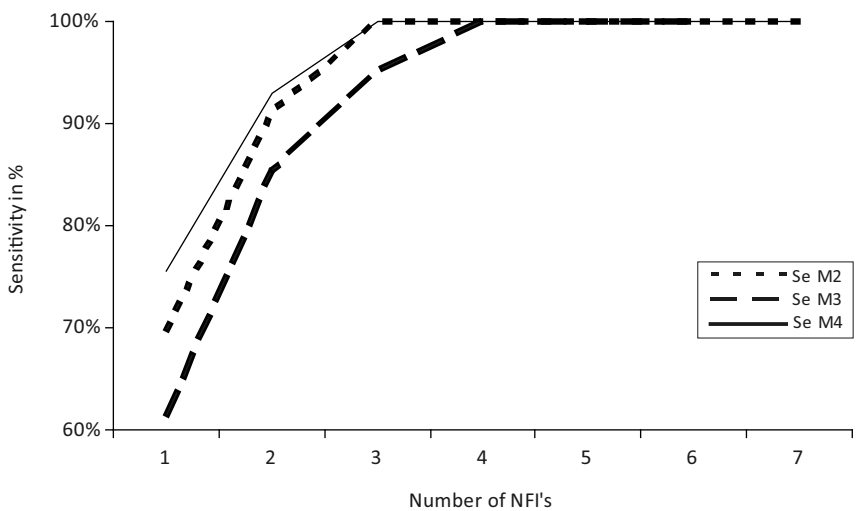

Figure 1. Relationship between number of NFI according to M1 and overall sensitivity of the three simplified test methods (M2, 3, 4).

DISCUSSION

This study examined the diagnostic accuracy of three simplified tests conducted by newly trained GHWs as compared to a reference test done by experienced physiotherapists. As leprosy control shifts towards integration in general health services, there is a need for simple, but effective tests to diagnose NFI. Evidence of simplified tests which may be useful in an integrated setting is lacking. The present study fills a gap in providing data on three such tests.

Various issues arise from these findings. First, this study examined in essence the performance of simplified tests compared to a reference test in diagnosing the presence or absence of NFI. The question was whether the simplified tests were able to detect NFI or not, regardless of the patients' leprosy type (PB or MB). Leprosy type of patients was not collected, since it is not associated with the performance of the test. Knowledge of leprosy type might have biased the testers to pay more attention to MB patients who have a higher risk of developing NFI compared to PB patients [13].

The overall Se was relatively high and the overall Sp was relatively low compared to the Se and Sp of single component testing. This can be explained by the different criteria used for defining a positive result (presence of NFI). For the overall test a positive result was defined as diagnosing the presence of any NFI in a patient that M1 identified as having NFI, no matter where the NFI was located. With single component testing the definition of a positive result was restricted to one specific combination. The probability of finding any NFI (regardless of whether it is the actual one present or not) is higher than of finding a specific NFI, resulting in a higher Se but lower Sp. Changing the definition of a positive result will generally improve one but the other will decline.

Testing of eyes was in general not very sensitive. While M1 measured lid gap in millimetres, the simplified tests only observed or asked for the presence of lid gap, which appears to be a less sensitive method. While M3 was most accurate for detecting lid gap, the low prevalence (2%) of this type of NFI limits the reliability of this result.

M2 had low Se of foot up testing. Further analysis showed that three assessors scored 0% Se, while the other nine assessors scored either 100% Se or had 0% prevalence (no true positives). Excluding these three assessors increased Se to 100%.

M3 had low Se of finger out and thumb up testing with the majority of testers scoring ≤ 50% Se. Difficulties in interpreting what was meant by the question: "Is the thumb straight?" might have been a cause for this. Testers were advised to look at whether the thumb was 'straight up' when the wrist was extended back, however, as a combined action, this posture might be too 'crude' to adequately notice NFI for these test components simply by observation.

M4 had low Sp of thumb up testing and ST of hands and feet. Two assessors scored less than 50% Sp. In general, the majority of M4 assessors scored lower Sp on these test components than assessors of M2 and M3. It suggests that self-reporting of thumb up NFI and sensory NFI of hands and feet yields more false positives, meaning that patients were more inclined to say that they had signs or symptoms of NFI although M1 reported no NFI.

This study is, to our knowledge, the first one describing and comparing the performance of simplified diagnostic tests conducted by newly trained GHWs. While the study provides useful new information about simplified tests, we also see limitations.

We took the full assessment done by experienced physiotherapists as the reference test, meaning that we considered this test and these testers as giving the most accurate results. In practice, even this assessment will not give the correct diagnosis in all cases. Diagnostic accuracy in terms of sensitivity and specificity as reported here for the simplified tests should therefore be seen as agreement or disagreement between the test methods and the reference test, rather than as referring to a 100% correct diagnosis of presence of absence of NFI. Assessment with monofilaments and VMT is, however, generally still considered the best widely available assessment to screen for NFI in leprosy patients. It was recently found that changes in the MFT and VMT scores reflect physiological changes in affected nerves as detected with more advanced techniques, such as nerve conduction measures [14]. By virtue of being simpler, the simplified tests do not cover all the items of a full assessment. For comparison we had to simplify the outcomes by dichotomising variables, meaning a loss of information.

There was a wide variety of general health background, education and skill levels of testers. Inter-rater variability is therefore expected, but was not analysed in this paper. Testers sat a pre-training and a post-training knowledge test. All but one tester scored better on post-tests relative to pre-tests. We did not find a consistent association between pre-test scores or post-test scores and testing performance.

Motivation of testers may be a potential source of bias. Especially in integrated settings where time is limited, staff might be less motivated to do their tasks to a consistent quality level. This may affect the accuracy of testing, but was not formally assessed.

For this study, training and practice were deliberately limited, to reflect the real-life circumstances and limitations of GHWs. It is difficult to compare this study with previous ones where assessors were better trained and qualified in full assessment testing, and which suggested that experience and training are important to ensure the reliability of testing [4,5,8]. The question is whether more training to gain better skill and experience is feasible in integrated settings with time constraints and lower numbers of new leprosy patients.

Simplified, but accurate tests are of great importance for the detection and diagnosis of NFI in leprosy, particularly in the context of integrated health services where GHWs have time-constraints, numerous tasks and little or no experience with leprosy. Bearing the limitations of a GHW in mind, this study evaluated three simplified tests believed to be simple and easy to remember. Method 2 appears particularly promising in the hands of GHWs. In general, M2 missed less people with NFI, while M3 had less over-diagnosis of NFI. M4 was accurate in detecting people with NFI, but had many false positives. This raises the question whether a higher Se or a higher Sp is more important in an integrated setting. Early detection of NFI requires a highly sensitive tool [15]. High specificity is also important, because steroid treatment is complex and not without side-effects and should only be given when there is significant NFI [16].

The primary task of GHWs will often be to screen patients for NFI and to refer patients detected with NFI to a doctor who will decide whether to treat or not. In this situation, both high Se and Sp are relevant. On the one hand, one does not want to miss any people with NFI who need treatment to prevent further disability. On the other hand, referring too many people who do not actually have NFI increases the risk that people will be treated unnecessarily with steroids and increases the workload of doctors. The final decision for treatment requires doctors who are able to recognise the signs and symptoms of NFI and are aware of steroid treatment for NFI and its adverse effects with prolonged use.

The absolute number of cases incorrectly diagnosed by GHWs with the different simplified tests depends on the number of newly detected cases with leprosy. For example, assume that there are 2000 new patients in a year of which 400 have or develop NFI (20%) and 1600 have no NFI (80%). When taking only the most commonly diagnosed types of NFI (sensory NFI of hands and feet, motor NFI of ulnar and median nerve) into consideration, M2 is projected to miss 96 people and over-diagnose 288 people. M3 would miss 108 people and over-diagnose 176 people. M4 would miss 56 people and over-diagnose 848 people. One has to bear in mind that this is only a fictitious calculation to gain insight in the implications of using these simplified tests with the given accuracy.

The main objective of the simplified tests is to screen for NFI in newly diagnosed patients. If any NFI was found by the simplified tests, they would be referred for further assessment and management. The simplified tests are not meant to replace thorough assessment; they merely indicate a need for it. The simplified tests are primarily useful in screening for NFI, and are not detailed enough to effectively monitor for small changes in NFI. M2 grades NFI and so may detect some changes in NFI severity, whilst M3 and M4 only indicate whether NFI is present or absent.

This study's primary question was: which simplified test is most useful in the hands of GHWs in terms of sensitivity and specificity? The results show that at the level of diagnosing the presence of any NFI a simplified version of the full assessment (M2) and a posture derived from an Indian dance (M3) are the most accurate simplified tests with M2 being more sensitive and M3 more specific. M4 had the highest sensitivity, but the lowest specificity. When looking at the single test components, M2 was more or similarly accurate in diagnosing the presence of the most common types of NFI (sensory NFI of hands and feet, motor NFI of ulnar and median nerve), compared to M3 and M4. M3 does not test at all for sensory NFI of the hands. M3 has to our knowledge not been tested outside India and it is unknown whether it could be applied in other countries or settings. We consider M2 (as proposed in ILEP Learning Guide Two) as the most useful simplified diagnostic test in the hands of GHWs with limited time and many responsibilities in an integrated context.

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Annex. Methods

Table I. Test components within each method.

	M1 (Reference)	M2 (ILEP)	M3 (Indian dance)	M4 (Questionnaire)
ST feet	10 pts (MF)	4 pts (BP)	stroking feet	yes/no
ST hands	10 pts (MF)	4 pts (BP)	-	yes/no
L. finger out	0-5 MRC	S-W-P	yes/no	yes/no
Foot up	0-5 MRC	S-W-P	yes/no	yes/no
Thumb up	0-5 MRC	S-W-P	yes/no	yes/no
Wrist up	0-5 MRC	-	yes/no	-
Eyeclosure	0-5 MRC	S-W-P	-	-
Eyelid gap	mm	yes/no	yes/no	yes/no

MF: monofilaments BP: ballpoint pen MRC: Medical Research Council grading S-W-P: strong-weak-paralysed

Table II. Definition of nerve function impairment (NFI) by method.

	Sensory NFI	Motor NFI
M1	≥ 2pts loss of feeling in any nerve	score < 4 (MRC)
M2	≥ 1pt loss of feeling in any hand/foot	score < 'Strong'
M3	no feeling in either foot	not able to do any of the posture movements
M4	reported loss of feeling in hands or feet	'no' on any questions

Voluntary muscle test:

Right	Strength testing:	Left
mm	Light eye lid closure	mm
	Strong eye closure	
Yes / No	Blink /Corneal sensation	Yes / No
	Other eye defects *	
	Little finger out +	
	Thumb up+	
	Wrist up+	
	Foot up+	

**Other eye defects*
Corneal ulcer = CU
Corneal Opacity = CO
Iritis = I
Scleritis = Sc
Cataract = Ca
Red eye = Red

+ Muscle strength
MRC grading 0 – 5

Sensory test:

Test 10 points using ballpoint pen or monofilament. If the client feels mark with a tick, if not, mark with a cross.

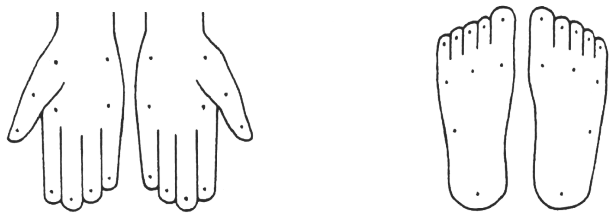

Figure I. M1 full assessment

Voluntary muscle test:

Right	Muscle Strength	Left
	Strong eye closure	
Yes / No	Lid gap on gentle closure	Yes / No
	Little finger out	
	Thumb up	
	Foot up	

Muscle strength
S = Strong / Normal
W = Weak
P = Paralysed

Sensory test:

Test 4 points using ballpoint. If the client feels mark with a tick, if not, mark with a cross.

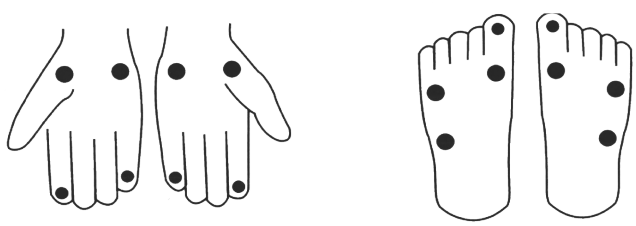

Figure II. M2 ILEP Learning Guide 2

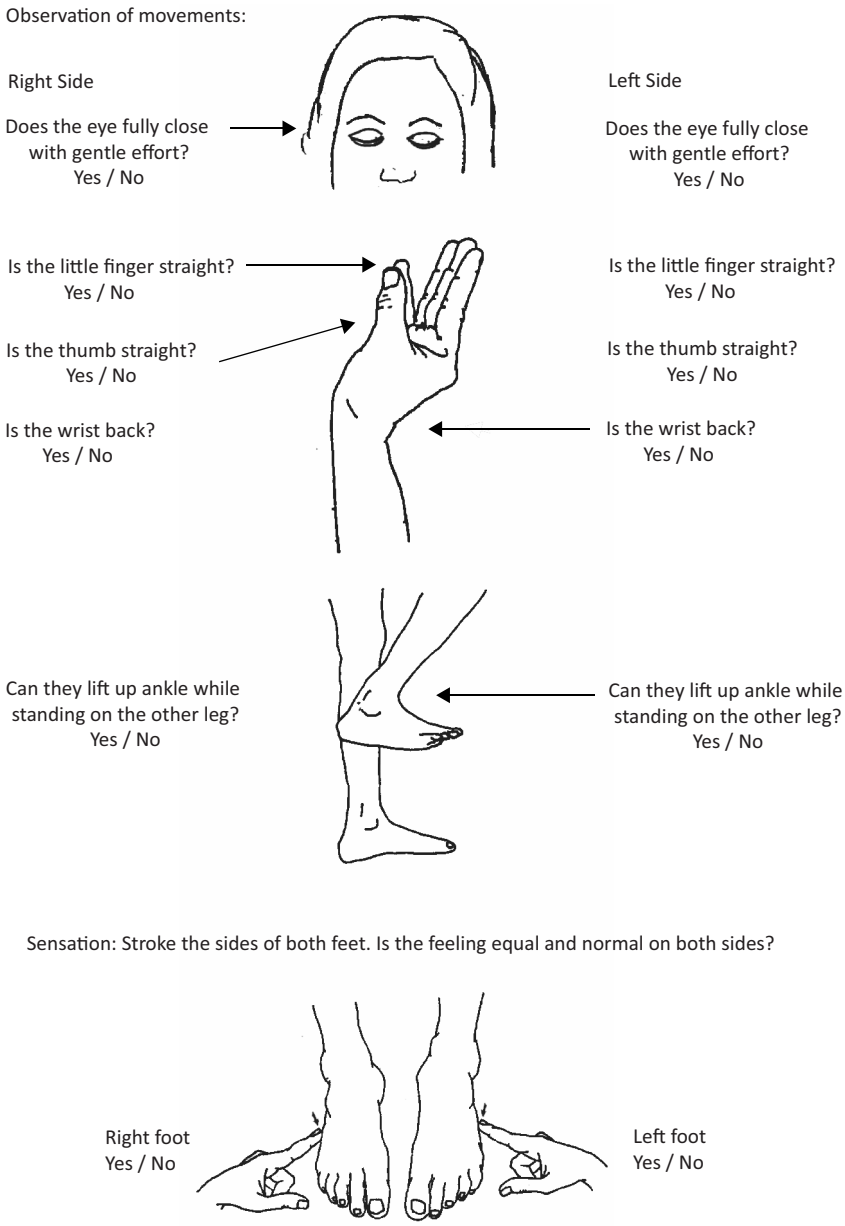

Figure III. M3 Indian dance

OBSERVATIONS		
Is there a gap when closing either eye?	NO	YES
Is there a red eye?	NO	YES
Are the fingers clawed (curled)?	NO	YES
Is there a foot drop (weakness in the foot so that person cannot lift up foot as he walks)?	NO	YES
Is there an ulcer on the hand or the foot	NO	YES
QUESTIONS		
Is there any nerve pain, burning or tingling in the hands or feet?	NO	YES
Is there any part of the body that does not have feeling?	NO	YES
Is the sight from either eye very poor (cannot count fingers at 6 metres)?	NO	YES
Is there any other problem in either eye (e.g. pain, watering)?	NO	YES
Is there any loss of feeling in the hands?	NO	YES
Does the person have difficulty touching his thumb and little finger together whilst keeping them straight?		
Is there any loss of feeling in the feet?		
Does the person have difficulty standing on his heels, with support?	NO	YES

Figure IV. M4 questionnaire

CHAPTER 5

Corticosteroids for treating nerve damage in leprosy. A Cochrane review

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SUMMARY

Background: Corticosteroids are commonly used for treating nerve damage in leprosy. We assessed the effectiveness of corticosteroids for treating nerve damage due to leprosy.

Methods: A systematic search was undertaken to identify randomised controlled trials (RCTs) comparing corticosteroids with placebo or with no treatment. Two authors independently assessed quality and extracted data. Where it was not possible to perform a meta-analysis, the data for each trial was summarised.

Findings: Three RCTs involving 513 people were found. Two trials compared prednisolone with placebo. One trial treated mild sensory impairment of less than six months duration and the other trial treated nerve function impairment of 6 to 24 months duration. Both trials examined nerve function improvement 12 months from the start of treatment, but found no significant difference between the two groups. The third trial compared three corticosteroid regimens for severe type 1 reactions. After 12 months, a significantly higher proportion of individuals on a 3 month course required extra corticosteroids compared to the groups with a high-dose and low-dose regimen of 5 months duration. Diabetes and peptic or infected ulcer were sometimes reported as serious adverse events in the placebo-controlled trials, but not significantly more often in the corticosteroid than placebo groups.

Interpretation: Evidence from two RCTs did not show a significant long-term effect for either long-standing nerve function impairment or mild sensory impairment. A third trial showed significant benefit of a five month steroid regimen over a three month regimen. Further RCTs are needed to establish the effectiveness and optimal regimens of corticosteroids and to examine new therapies.

INTRODUCTION

This paper is based on a Cochrane review first published in The Cochrane Library 2007, Issue 2 (see http://www.thecochranelibrary.com/ for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

Corticosteroids, especially prednisolone, are commonly used for treating severe reactions and nerve damage in leprosy. They work by controlling the acute inflammation and relieving the pain [1,2]. The earlier corticosteroids are given after onset of nerve damage, the more likely permanent nerve function impairment will be prevented [3,4]. The recommended corticosteroid regimen for treating nerve damage starts with 40 mg prednisolone daily and lasts for 12 weeks [5]. Studies indicate that prolonged prednisolone treatment may be more effective in treating severe reactions and nerve damage [3,6-8]. Prednisolone seems to be a very effective drug, but it has some shortcomings. Long-term therapy may cause serious adverse effects, such as peptic ulcer, cataract, or psychosis [9-11]. A considerable proportion of people treated for nerve damage does not benefit from corticosteroid treatment [12-15]. Other therapies for improving nerve function and relieving nerve pain, such as surgical decompression of nerves [16-18], azathioprine [19], and ciclosporin [20], have been tested. These interventions are beyond the scope of this review.

Corticosteroids are the drugs of choice for acute severe reactions and nerve damage, but the long-term effect of corticosteroids is uncertain and the optimal regimen has not been established. While this review focused on evidence from randomised controlled trials (RCTs), it was expected that only a few RCTs have been conducted in this area. Therefore, the results have also been considered in the light of non-randomised evidence in the Discussion section.

METHODS

Search strategy

We searched the Cochrane Neuromuscular Disease Group Register using the following terms: (leprosy or Hansen disease or Hansen's disease) AND (steroid* or corticosteroid* or glucocorticoid* or (cortical hormone*) or prednison* or prednisolon* or cortison*) AND ((exp peripheral nervous system diseases) or neuritis or neuropath* or (nerve damage) or (nerve involvement) or (nerve loss) or (nerve function impairment) or (nerve problem*) or (sensory loss) or (motor loss) or (nerve pain) or (nerve tenderness) or reaction*). This search strategy, combined with a search strategy for identifying randomised trials, was adapted to include additional search terms where necessary and was modified to search the Cochrane Central Register of Controlled Trials (*Cochrane Library*, Issue 4, 2007), MEDLINE (from 1966), EMBASE (from 1980), CINAHL (from 1980) and LILACS (from 1982) in January 2008. References from trials and conference proceedings were searched. Trial authors were contacted and the Current Controlled Trials Register (www.controlled-trials.com) was searched

for ongoing trials. There were no language restrictions. Two authors independently screened the titles and abstracts of all the publications identified to examine whether studies were eligible.

Study selection

Studies were eligible if they were (quasi-) randomised controlled trials (RCTs) assessing corticosteroids versus placebo or no treatment for patients with leprosy and related nerve damage or severe leprosy type 1 reaction, requiring corticosteroid treatment. Nerve damage or nerve function impairment (NFI) was defined as clinically detectable impairment of motor or sensory nerve function. It did not include impairment of nerve conduction that was only detectable by electrophysiological means [21]. Outcome measures of interest were: improvement in sensory nerve function as measured with graded nylon filaments [22] or a ball-point pen after one or two years, improvement in motor nerve function, assessed with the modified MRC grading scale [23] after one or two years, change in nerve pain and tenderness after one year, and adverse events requiring withdrawal from treatment.

Methodological quality

The methodological quality of the included studies was based on the following criteria: concealment of allocation; blinding of participants and outcome assessors; loss to follow-up; clear diagnosis; baseline differences and explicit outcome measures mentioned. Each criterion was assessed as A: adequate, B: unclear or C: inadequate. If one of the criteria was not described in the study, it was labelled 'inadequate'. Concealment of allocation was considered adequate if the randomisation process prevented the individual making the allocation from foreseeing the treatment assignment. Blinding was considered adequate if participants and outcome assessors were unaware of the treatment given. Follow-up was considered adequate if the loss to follow-up was less than 10%. Two authors independently assessed the included studies for methodological quality.

Data extraction and analysis

Two authors extracted data regarding methodology and outcome measures from the included studies onto a data extraction form. If there were missing data, the trial authors were contacted. Authors were not blinded to trial author, journal or institution. We used the Cochrane statistical package, Review Manager, for statistical data analysis. Results were expressed as mean differences with 95% confidence intervals (CI) for continuous outcome measures and relative risks (RR) with 95% CI for dichotomous outcomes. In case of clinical heterogeneity, or if data were lacking, the results for each trial were summarised. We analysed separately participants with NFI of less than six months duration and participants with long-standing impairment (6 to 24 months duration). Adverse effects were expressed as the proportion of participants with major adverse events.

RESULTS

Study selection

We identified ten potentially relevant studies and excluded eight, because they were not randomised, compared corticosteroids plus a complementary therapy versus corticosteroids, or focused on prevention of nerve damage. One RCT became available during the review process. In total, we found three RCTs for this review. The characteristics of the included studies are shown in table 1.

Interventions

Two studies compared corticosteroids with placebo. One of them compared prednisolone with placebo in participants with mild sensory NFI [24]. The other trial compared prednisolone with placebo in participants with long-standing NFI [25]. One study compared three different corticosteroid regimens [26]. This trial compared high dose corticosteroids versus low dose corticosteroids versus short regimen corticosteroids for participants with severe type 1 reactions.

Outcome measures

The two trials comparing corticosteroids with placebo assessed improvement of nerve function one year after the start of treatment. Improvement was measured as either a change score between baseline and end of follow-up or as the proportion of participants improved. Change in nerve pain and nerve tenderness was not measured in these trials. Adverse events, requiring withdrawal of treatment were reported in both trials.

None of the pre-specified outcome measures were evaluated in the trial comparing three different corticosteroid regimens. The primary endpoint was the requirement for additional corticosteroids during the 12 months trial period. A poor outcome was defined as a failure to respond to treatment in terms of changes to skin lesions, nerve pain or tenderness, or nerve function, or recurrences of skin or nerve lesions and needing extra corticosteroids.

Methodological quality

Randomisation and blinding were considered adequate in all three trials. Loss to follow-up varied from 3% to 19%. Leprosy was diagnosed and classified leprosy using skin smear or number of skin lesions. Baseline characteristics in the different groups were similar. Nerve function improvement after one year was reported in two trials, but not after two years. Change in nerve pain and nerve tenderness was not measured in any of the trials. Adverse events occurred in two trials.

Table 1. Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes
Rao 2006	Randomised, parallel group trial. Externally controlled computer randomisation. Double blind.	334 leprosy patients with severe type 1 reactions, defined as nerve tenderness, any motor or sensory NFI of duration less than 3 months, or severely inflamed skin lesions, requiring steroid treatment. Persons randomised: 334. Persons analysed: 269 (a: 88, b: 91, c: 90).	(a) Prednisolone start at 60 mg/day and thereafter gradually tapered with 10 or 5 mg/2 or 4 weeks until 5 months completed (total 3500 mg). (b) Prednisolone start at 30 mg/day and thereafter gradually tapered with 5 mg/2, 4 or 8 weeks until 5 months completed (total 2310 mg). (c) Prednisolone start at 60 mg/day and thereafter gradually tapered with 20 or 10 mg/2 weeks until 3 months completed (total 2940 mg) plus 2 months placebo.	1) Requirement for additional corticosteroids during the 12-month trial period	Multicentre. Conducted in six centres in India
Richardus 2003	Randomised, parallel group trial. Externally controlled computer randomisation. Double blind.	95 leprosy patients with confirmed MB leprosy diagnosis having untreated sensory or motor impairment of the ulnar or posterior tibial nerve of more than 6 months up to 24 months of duration. Unit of randomisation: person. Unit of analysis: ulnar or posterior tibial nerve. Of participants with bilateral nerve function impairment, the scores of the most affected limb were used in the analysis. If both limbs were equally affected, then the scores of the right side were used in the analysis. Persons randomised: 95. Nerves analysed: 92 (a: 41, b: 51).	(a) Prednisolone start at 40 mg/day and thereafter gradually tapered with 5 mg/2 weeks until 16 weeks completed (total 2520 mg) b) Placebo, equivalent number of tablets for 16 weeks	1) Sensory improvement after 1 year 2) Motor improvement after 1 year 3) Occurrence of major adverse events	Multicentre. Conducted in Nepal and Bangladesh. TRIPOD 3.

Table 1 Continued

Study	Methods	Participants	Interventions	Outcomes	Notes
van Brakel 2003	Randomised, parallel group trial. Externally controlled computer randomisation. Double blind.	84 leprosy patients with confirmed MB leprosy diagnosis having sensory impairment of the ulnar or posterior tibial nerve of less than 6 months duration Unit of randomisation: person. Unit of analysis: ulnar or posterior tibial nerve. Of participants with bilateral nerve function impairment, the scores of the most affected limb were used in the analysis. If both limbs were equally affected, then the scores of the right side were used in the analysis. Persons randomised: 84. Nerves analysed: 75 (a: 41, b: 34).	(a) Prednisolone start at 40 mg/day and thereafter gradually tapered with 5 mg/2 weeks until 16 weeks completed (total 2520 mg) (b) Placebo, equivalent number of tablets for 16 weeks	1) Sensory improvement after 1 year 2) Occurrence of major adverse events	Multicentre. Conducted in Nepal and Bangladesh. TRIPOD 2.

Corticosteroids versus placebo for participants with mild sensory nerve function impairment (NFI) of less than six months duration [24]

Results were available for 89% (75/84) of the participants. After 12 months the mean change in sensory score was -2.68 ± 2.66 in the prednisolone group and -3.00 ± 2.75 in the placebo group both implying a mean improvement. The improvement was slightly greater in the placebo group but the mean difference 0.32 (95% CI -0.91 to 1.55) between the two groups was not significant. The proportion with sensory improvement was 80% (33/41) in the prednisolone group compared with 79% (27/34) participants in the placebo group. The difference was not significant (relative risk 1.01, 95% CI 0.81 to 1.27). Major adverse events were reported in two participants. One person was diagnosed with diabetes (prednisolone) and one with an infected ulcer (placebo).

Corticosteroids versus placebo for participants with long-standing nerve function impairment (NFI) of 6 to 24 months duration [25]

Results were available for 94% (89/95) of the participants. After 12 months the mean difference in sensory score was -1.25 ± 1.66 in the prednisolone group and -1.67 ± 3.02 in the placebo group indicating a mean improvement in both. The improvement was slightly greater in the placebo group but the mean difference 0.42 (95% CI -0.57 to 1.41) between the two groups was not significant. The proportion with sensory improvement was 57% (17/30) in the prednisolone group compared with 59% (24/41) in the placebo group (results available for 71 participants). The difference was not significant (relative risk 0.97, 95% CI 0.65 to 1.45). Results of motor nerve function were available for 21 participants. Of these 21 participants, 3 had motor NFI only and 18 had both sensory and motor NFI. After 12 months the mean difference in motor score was -0.18 ± 0.98 in the prednisolone group and -0.30 ± 1.06 in the placebo group both indicating a mean improvement. The improvement was slightly greater in the placebo group but the mean difference 0.12 (95% CI -0.76 to 1.00) between the two groups was not significant.
Five participants came out of the trial due to symptoms of possible major adverse events. Three of them were in the prednisolone group (diabetes, infected ulcer, 'hypersensitivity' to the tablets), and the other two were assigned to placebo treatment (diabetes, peptic ulcer).

High dose corticosteroids versus low dose corticosteroids versus short regimen corticosteroids for participants with severe type 1 reactions [26]

At the end of the 12 month period, 41 out of 90 participants (46%) in the short course group (2940 mg over 3 months) needed extra corticosteroids. In the group of participants receiving a low dose of prednisolone (2310 mg over 5 months) this was 28 out of 91 (31%) and 21 out of 88 participants (24%) following a high dose prednisolone regimen (3500 mg over 5 months) required additional prednisolone. The difference between the high dose and low dose 5 month regimen was not significant (relative risk 0.78, 95% CI 0.48 to 1.26). The relative risk of needing additional corticosteroids was significantly less with the high dose 5 month course than with the

3 month course (relative risk 0.52, 95% CI 0.34 to 0.81). The relative risk of needing additional corticosteroids was just significantly less with the low dose 5 month course than with the 3 month course (relative risk 0.68, 95% CI 0.46 to 0.99). No major adverse events were reported during the follow-up period of this trial.

DISCUSSION

Three randomised controlled trials were available for this review. The interventions and outcomes were too heterogeneous to be entered in a meta-analysis. The numbers of participants included in the trials were small and did not allow for subgroup analysis.

The variability between studies and the limitations in sample size made it difficult to draw any robust conclusions. None of the trials found a significant difference in improved nerve function between treatment and control group twelve months after the start of treatment. The question, whether corticosteroids are beneficial in treating acute NFI or type 1 leprosy reaction in a field setting in the longer term compared to placebo, remains unclear.

Several non-randomised studies have examined the effect of corticosteroids for treating severe reactions and nerve damage in leprosy. The response to corticosteroid treatment seems to depend on the severity and duration of NFI before the start of treatment.

One study found that 35% of patients having complete anaesthesia and 67% with moderate sensory impairment improved to good function three months after the start of corticosteroid treatment. For patients with complete motor paralysis or moderate motor impairment, respectively 11% and 55% of the patients recovered to good function [27]. The RCT of treating mild sensory impairment found that a significant higher proportion improved in the prednisolone group compared to the placebo group after four months, although the difference disappeared by the 6-month follow-up [24]. Another study found that it may take a long time to achieve full recovery of chronic or recurrent NFI, at least much longer than the duration of a standard steroid course [14]. Recovery of nerve function loss is more likely when the duration of NFI has been less than six months [2,3]. To illustrate, data from Ethiopia showed that patients with NFI for less than six months and treated with steroids had full recovery in 50 out of 57 nerves (88%), while in patients with recurrent or chronic NFI only 20 out of 39 nerves (51%) had fully recovered after up to ten years after treatment [14]. This is in line with the RCT of treating long-standing NFI which found that 19 out of 41 nerves (46%) treated with prednisolone improved [25]. However, even in the placebo group, 25 out of 51 nerves (49%) showed spontaneous improvement after 12 months. Other studies also reported spontaneous nerve function improvement in untreated individuals [12,14,15].

The optimal corticosteroid regimen has not been established. Recommendations about the optimal dose and duration of steroid therapy have changed over time [8,28]. The principles of a steroid therapy are that it should start with a dose that is sufficient to control the inflammation rapidly.

Then the dose should be tapered off until the reaction has settled. The ideal would be a steroid course adjusted and tailored to the individual's situation, but this may be only possible in referral centres [29].

Currently, a standard 12-week course of prednisolone is recommended by the WHO which can be safely used in the field [5]. Other studies have suggested that a prolonged regimen might be more beneficial. One small retrospective study compared a short-term steroid treatment (two months) with a prolonged steroid treatment (3 to 18 months) for type 1 reaction in borderline leprosy patients. It was found that the latter treatment gave better results on improving motor nerve function than the shorter treatment and did not increase the risk of adverse events. The critical dose to control a reaction after the initial period was considered to be 15 to 20 mg daily [7]. One study examined the effects of prednisolone treatment on the cellularity and cytokine profiles of leprosy type 1 reactions. The results showed that prednisolone treatment decreased cytokine levels significantly only after 28 days from the start of treatment. Some patients continued to have cytokine production for one to six months. This study illustrates the slow response to steroid therapy and continuing activity for several months [6]. While these non-randomised studies already suggested the benefits of a prolonged steroid course, the RCT comparing three corticosteroid regimens confirms this in reporting that a longer duration of prednisolone treatment gave less poor outcomes than a short course of prednisolone [26].

According to other authorities, a substantial proportion of individuals treated for nerve damage do not respond to corticosteroids. The overall nerve function improvement levels vary approximately between 60% and 80% after steroid therapy [12]. This study reported that 27 out of 83 treated nerves with motor impairment (33%) and 53 out of 166 treated nerves with sensory impairment (32%) did not improve or had deteriorated twelve months after the start of treatment. In a study in Thailand, 27 out of 77 patients who were treated with prednisolone (35%) showed no improvement or a worsening of NFI [15]. One randomised controlled trial examined the effect of prophylactic use of steroids in 636 newly diagnosed multibacillary patients [30]. This study showed that a low dose prophylactic steroid regimen reduced the risk of NFI at the end of four months, but the effect was not sustained at one year. Repeat use of steroid prophylaxis for a longer period than four months may sustain the benefit, but this needs to be further examined.

An alternative therapeutic approach for treating nerve damage in leprosy has been surgical decompression of acutely inflamed nerves. There is an ongoing search for new therapies, because steroids are not always effective, and may cause serious adverse effects and because their long-term effect is unclear. A quasi-randomised controlled trial compared an eight-week course of prednisolone combined with azathioprine with a 12-week course of prednisolone alone for treating severe type 1 reactions [19]. The trial did not find a significant difference between the two treatment groups, but the study was limited in size (n=40). A recent non-randomised follow-up study assessed the effects of ciclosporin treatment in 33 Ethiopian and 10 Nepali leprosy patients with severe type 1 reactions and the authors suggested that ciclosporin monotherapy may be an

effective treatment for severe type 1 reactions with few adverse effects [20]. Therapies which are used for other immune-mediated conditions, such as ciclosporin or combinations of immunosuppressants may be promising. It is plausible that these therapies may be effective for treating nerve damage in leprosy, but evidence from RCTs is lacking [1].

CONCLUSION

Implications for practice

Evidence from the three randomised controlled trials is insufficient to draw robust conclusions about the long-term effect of corticosteroids for treating nerve damage in leprosy. Two trials, of which one treated long-standing nerve function impairment and the other mild sensory impairment, did not show significantly better outcomes with corticosteroids than placebo for treating nerve damage in the long term. However in a third trial, a 5 month corticosteroid regimen was significantly more beneficial than a 3 month corticosteroid regimen. Standard corticosteroid regimens are not significantly more harmful than placebo treatment, despite known adverse effects of corticosteroids.

Implications for research

There is a need for high-quality randomised controlled trials to establish the value and optimal dose of corticosteroid regimens and to examine the efficacy and safety of new therapies. Future trials should pay more attention to non-clinical aspects, such as costs and impact on quality of life, because these are highly relevant indicators for both policy makers and participants.

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CHAPTER 6

Decompressive surgery for treating nerve damage in leprosy. A Cochrane review

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SUMMARY

Background: Decompressive surgery is used for treating nerve damage in leprosy. We assessed the effectiveness of decompressive surgery for patients with nerve damage due to leprosy.

Methods: A broad search strategy was performed to find eligible studies, selecting randomised controlled trials (RCTs) comparing decompressive surgery alone or plus corticosteroids with corticosteroids alone, placebo or no treatment. Two authors independently assessed quality and extracted data. Where it was not possible to perform a meta-analysis, the data for each trial was summarised.

Findings: We included two randomised controlled trials involving 88 people. The trials examined the added benefit of surgery over prednisolone for treatment of nerve damage of less than six months duration. After two years follow-up there was no significant difference in nerve function improvement between people treated with surgery plus prednisolone or with prednisolone alone. Adverse effects of decompressive surgery were not adequately described.

Interpretation: Evidence from randomised controlled trials does not show a significant added benefit of surgery over steroid treatment alone. Well-designed randomised controlled trials are needed to establish the effectiveness of the combination of surgery and medical treatment compared to medical treatment alone.

INTRODUCTION

This paper is based on a Cochrane review first published in The Cochrane Library 2009, Issue 1 (see http://www.thecochranelibrary.com/ for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

Decompressive surgery or neurolysis as treatment for nerve damage has been done for several decennia. The objective of this surgery is to relieve mechanical compression, due to oedema caused by neuritis, of the affected nerve. Decompression is done by incision of the thickened nerve sheath (epineurium) where the nerve is enlarged and often tender on palpation. This incision is often of a considerable length at the place before entering the fibro-osseous tunnel which, during surgery, needs to be opened as well. Results of surgery from non-randomised studies have been widely published [1-6]. Decompressive surgery is not recommended without medical treatment. Indications for surgery are mainly based on common practice but not well-defined. These may include the presence of nerve abscess, nerve pain or nerve function impairment that does not respond to medical treatment [7-11].

Decompressive surgery is frequently used for treating nerve damage in leprosy. The effect of surgery, especially in the long-term, is uncertain and it is unclear whether surgery is more beneficial than medical treatment alone. While this review focused on evidence from randomised controlled trials (RCTs), it was expected that only a few RCTs have been conducted in this area. Therefore, the results were also considered in the light of non-randomised evidence in the Discussion section.

Methods

Search strategy

We searched the Cochrane Neuromuscular Disease Group Trials Register (November 2007) using the following terms: leprosy or Hansen disease and decompression or neurolysis or epicondylectomy or epineurotomy or neuritis or nerve damage or nerve loss or nerve function impairment or neuropath* or nerve problem or nerve involvement or nerve pain. This search strategy, combined with a search strategy for identifying randomised trials, was adapted to include additional search terms where necessary and was modified to search the Cochrane Central Register of Controlled Trials in *The Cochrane Library* (Issue 4, 2007); MEDLINE (from January 1950 to November 2007) and EMBASE (from January 1980 to November 2007); AMED (Allied and Complementary Medicine, from January 1985 to November 2007), CINAHL (from January 1982 to November 2007), and LILACS (Latin American and Caribbean Health Science Information database, from January 1982 to November 2007). We checked reference lists of the studies identified, the Current Controlled Trials Register (www.controlled-trials.com), conference proceedings and contacted trial authors. There

were no language restrictions. Two authors independently screened the titles and abstracts of all the publications identified to examine whether studies were eligible.

Study selection

Studies were eligible if they were (quasi-) randomised controlled trials (RCTs) assessing decompressive surgery versus corticosteroids, placebo or no treatment for patients with leprosy and related nerve damage. Nerve damage or nerve function impairment (NFI) was defined as clinically detectable impairment of motor or sensory nerve function. It did not include impairment of nerve conduction that was only detectable by electrophysiological means [12]. Outcome measures of interest were: improvement in sensory nerve function as measured with graded nylon filaments [13] or a ball-point pen after one or two years, improvement in motor nerve function, assessed with the modified MRC grading scale [14] after one or two years, change in nerve pain and tenderness after one year, changes in quality of life, and adverse events

Methodological quality

The methodological quality of the included studies was based on the following criteria: concealment of allocation; blinding of participants and outcome assessors; loss to follow-up; baseline differences and explicit outcome measures mentioned. Each criterion was assessed as A: adequate, B: unclear or C: inadequate. If one of the criteria was not described in the study, it was labelled 'inadequate'. Two authors independently assessed the included studies for methodological quality.

Data extraction and analysis

Two authors extracted data regarding methodology and outcome measures from the included studies onto a data extraction form. If there were missing data, the trial authors were contacted. Authors were not blinded to trial author, journal or institution. We used the Cochrane statistical package, Review Manager, for statistical data analysis. Results were expressed as mean differences with 95% confidence intervals (CI) for continuous outcome measures and relative risks (RR) with 95% CI for dichotomous outcomes. In case of clinical heterogeneity, or if data were lacking, the results for each trial were summarised.

RESULTS

Study selection

We identified ten potentially relevant studies and excluded seven, because they were not randomised. Two RCTs (one RCT was described in two papers) were included. Characteristics of the included studies are shown in table 1.

Table 1. Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes
Boucher 1999	Randomised, parallel group trial. Randomisation by a computer random number table. Blinding not possible.	31 leprosy patients with nerve deficit < 6 months duration. Unit of randomisation: ulnar, median, common peroneal, or posterior tibial nerve. Unit of analysis: nerve. Nerves randomised: unclear. Nerves analysed: 93 (a: 47 , b: 46)	(a) prednisone start at 40 mg/day for 15 days and thereafter gradually tapered with 5 mg/15 or 30 days until 6 months completed (total 3450 mg). (b) same intervention plus external nerve decompression and a simple, longitudinal epineurotomy.	1) Sensory improvement after 2 years Motor improvement after 2 years Nerve pain after 2 years	Single centre. Conducted in Senegal.
Ebenezer 1996 / Pannikar 1984	Randomised, parallel group trial. Randomisation by alternation. Blinding not possible.	57 leprosy patients with ulnar neuritis < 6 months duration. Unit of randomisation: person. Unit of analysis: ulnar nerve. Persons randomised: 57 with 75 ulnar nerves (18 bilateral cases). Nerves analysed: 62 of 44 persons (a: 31, b: 31) after one year, 57 of 39 persons (a: 28, b: 29) after two years	(a) prednisolone 30 mg/day for one week, reducing the daily dose by 5 mg every week for 6 weeks (total 735 mg). (b) same intervention plus external nerve decompression and a simple, subperiosteal medial epicondylectomy.	1) Sensory improvement after 1 and 2 years 2) Motor improvement after 1 and 2 years	Single centre. Conducted in India.

Interventions

Both studies tested decompressive surgery plus oral corticosteroids versus oral corticosteroids alone. One tested treatment of ulnar neuritis of less than six months duration [15,16] and one tested treatment of neuritis of several types of less than six months duration [17].

Outcome measures

The primary outcomes 'improvement in sensory nerve function one year after registration' and 'improvement in motor nerve function one year after registration' were evaluated in one trial [15]. The secondary outcome 'improvement in nerve function two years after registration' was evaluated in two trials [16,17]. 'Change in nerve pain and in nerve tenderness' was assessed one year after registration in one trial [15] and two years after registration in two trials [16,17]. None of the trials evaluated 'changes in quality of life'. Adverse events were not well-reported in any of the trials.

Methodological quality

Randomisation was considered adequate in one trial [17], while the other trial used alternation as randomisation procedure which was considered inadequate [15,16]. Participant and clinician blinding was not possible in any of the trials. One trial [17] had 6% loss to follow-up of participants, but did not report how many nerves were involved. The other trial [15,16] had 17% loss to follow-up of nerves after one year and 24% loss to follow-up of nerves after two years. None of the trials reported how many participants or nerves were lost to follow up in each arm.

Boucher et al. described the reasons for losses. Baseline characteristics in both treatment arms were similar in the trials.

Medial epicondylectomy plus oral corticosteroids versus oral corticosteroids alone for participants with ulnar neuritis of less than six months duration [15,16]

Results were available for 77% (44/57) of the participants. After one year the mean difference in sensory score was 2.08 (95% CI 0.28 to 3.88) in the surgery group and 2.00 (95% CI 0.06 to 3.94) in the medical group indicating a mean sensory improvement in both. The improvement was slightly greater in the surgery group but the mean difference 0.08 (95% CI -2.45 to 2.61) between the two groups was not significant. In the surgery group 18 out of 31 nerves (58%) had sensory improvement after one year compared with 16 out of 31 nerves (52%) in the medical group. The difference was not significant (relative risk 1.30, 95% CI 0.48 to 3.54).

Results of changes in motor nerve function were provided. After one year the mean difference in motor score was 3.08 (95% CI 2.12 to 4.04) in the surgery group and 2.26 (95% CI 0.21 to 4.31) in the medical group indicating a mean improvement in both. The improvement was greater in the surgery group but the mean difference 0.82 (95% CI -1.34 to 2.98) between the two groups was not significant. In the surgery group 20 out of 31 nerves (65%) had motor improvement after

one year compared with 22 out of 31 nerves (71%) in the medical group. The difference was not significant (relative risk 0.74, 95% CI 0.26 to 2.17).

Results after two years were available for 68% (39/57) of the participants. After two years the mean difference in sensory score was 2.89 (95% CI 0.94 to 4.84) in the surgery group and 2.91 (95% CI 0.73 to 5.09) in the medical group indicating a mean improvement in both. The improvement was slightly greater in the medical group but the mean difference -0.02 (95% CI -2.82 to 2.78) between the two groups was not significant. The mean difference in motor score after two years was 2.79 (95% CI 1.03 to 4.55) in the surgery group and 2.57 (95% CI 0.49 to 4.65) in the medical group indicating a mean improvement in both. The improvement was greater in the surgery group but the mean difference 0.22 (95% CI -2.39 to 2.83) between the two groups was not significant. Nerve pain and tenderness had disappeared in both groups after one year and no new nerve pain or tenderness between the first and second year was reported. The trial did not report any adverse events or reasons of loss to follow-up. Contacting the authors did not yield additional information.

Longitudinal epineurotomy plus oral corticosteroids versus oral corticosteroids alone for participants with neuritis of less than six months duration [17]

Results were available for 97% (30/31) of the participants. Outcomes were given after two years of follow-up and were expressed as median improvement, meaning that 50% of the data had greater improvement than this value and 50% of the data had less improvement than this median. In the surgery group median sensory improvement was 25% compared to 20% median improvement in the medical group. The difference was not significant at a 5% level (Tukey box plot test). Median motor improvement was 30% in the surgery group and 20% in the medical group. The difference was not significant at a 5% level (Tukey box plot test). No numbers, test values or 95% confidence interval values were given. In the surgery group median nerve pain relief was 11% compared to 0% in the medical group. The difference was significant at a 5% level (Tukey box plot test). One participant was excluded from the study due to haemorrhage, but it was unclear if it was caused by the intervention. The study did not provide any numbers, test values or 95% confidence interval values. Contacting the author revealed that original data were not available anymore.

DISCUSSION

Two randomised controlled trials were available for this review. One trial compared the added benefit of medial epicondylectomy over corticosteroids for participants with ulnar neuritis of less than six months duration [15,16]. The other trial compared the added benefit of longitudinal epineurotomy over corticosteroids for participants with ulnar, median, common peroneal or posterior tibial nerve involvement of less than six months duration [17]. The interventions and outcomes were too heterogeneous to be combined in a meta-analysis. The numbers of participants included

in the trials were small and did not allow for subgroup analysis. The variability between studies and the limitations in study design and sample size made it difficult to draw any robust conclusions. None of the trials found a significant difference in improved nerve function between surgery and medical group after a follow-up of one or two years. This result may have been biased by the selection criteria used for inclusion of patients and nerves. Only a small proportion may benefit from decompressive surgery. Results from a study indicate that only 5-10% of nerves may improve after surgery (Naafs, personal communication). The other nerves need no decompression. By taking all nerves together, results may be diluted and the conclusion clouded.

The two trials had some drawbacks. One major drawback of both trials was that they used sometimes more than one nerve from individual patients in the analyses thereby considering the outcomes from each nerve independent. The trial of Pannikar and Ebenezer included 18 patients with ulnar nerve damage at both sides (bilateral involvement). The right side was allocated to the group drawn by random selection and the left side was allocated to the other group. The final results reflect the outcomes of all nerves. No separate analysis was done using only one independent outcome from each patient. Original data were not available. The trial of Boucher included 31 patients with 93 nerves in total. It was unclear how many nerves each patient contributed. The final results reflect the outcomes of all nerves. No separate analysis was done using only one independent outcome from each patient. Original data were not available. The results from these studies should be treated with considerable caution, because results from a patient contributing outcomes from more than one nerve will be treated, in the analysis, as having more weight as a patient contributing only one nerve.

Other limitations of the study of Pannikar were that randomisation was done by alternation, which is considered an inadequate randomisation procedure. With regard to loss to follow-up, 23% of the participants were lost to follow-up after one year and 32% after two years. No reasons for these losses were reported and no intention-to-treat analysis was performed.

The randomisation procedure and loss to follow-up (6%) were considered adequate in the study of Boucher. Outcomes were expressed as median improvement. No numbers or original data were available to calculate mean differences or relative risks making comparison and interpretation of the results difficult. Subgroup analyses showed no difference in median improvement between operated or non-operated nerves with respect to type of leprosy (lepromatous or non-lepromatous), type of antibacillary drug therapy (mono or multi), type of nerve function impairment (motor or sensory), and duration of neuritis (0-3 months or 3-6 months). There were significant differences for pain relief and severity of the neuritis before surgery. Operated nerves had higher median pain relief compared to non-operated nerves. In the group with considerable loss of nerve function the operated nerves had higher median improvement compared to non-operated nerves.

The occurrence of adverse effects was not adequately reported in the trials. One study [17] excluded a participant with haemorrhage during the course of the trial, but it was unclear whether this was due to the intervention. The literature reviewing decompressive surgery in leprosy often does

not take adverse effects into account, but stresses the importance of having adequate techniques and instruments and competent surgeons to prevent unfavourable outcomes [9,18,19]. Complications of decompressive surgery in general may be painful scars, wound problems, haematoma, infection and damage to nerves, arteries or tendons [20-22].

None of the trials included quality of life measures or cost-effectiveness calculations which could be useful indicators of the effectiveness of interventions.

Many published and unpublished non-randomised studies have examined the effect of decompressive surgery for treating nerve damage in leprosy. While the two RCTs give insufficient evidence in favour of decompressive surgery in addition to steroid treatment, most non-randomised studies report beneficial effects of decompressive surgery. Relief of nerve pain and tenderness is the most frequently and consistently reported benefit. Nerve function improvement is frequently reported, but the response to surgery seems to depend on several factors, such as severity and duration of neuritis before surgery, the type of leprosy, the nerve involved and the surgical technique used. Nerves which are partially damaged, have neuritis of less than six months duration and are associated with multibacillary (MB) leprosy show better results [7,8,10,11,23]. Studies examining the effects of surgery reported sensory improvement varying from about 38% to 97% and motor improvement varying from about 26% to 63% [2,3,6,18,24-34]. Comparison of these studies is difficult due to differences in surgical techniques used, duration and severity of neuritis, type of leprosy, follow-up time, and outcome measures.

Several non-randomised studies compared operated versus non-operated nerves. One study evaluated nerve function in nine individuals with neuritis of less than six months duration. Three patients underwent ulnar nerve decompression, three patients received corticosteroid therapy for ulnar neuritis and three patients underwent median nerve decompression. The study found an average nerve function improvement of 35% for ulnar nerve decompression (*n*=3), 32% for steroid treatment of eight weeks (*n*=3) and 18% median nerve decompression (*n*=3) six months after surgery or start of treatment [34].

Three studies examined surgery alone versus surgery plus steroids. One study compared medial epicondylectomy alone (*n*=7) with medial epicondylectomy plus steroids (*n*=7) given two weeks post-operatively for ulnar neuritis of less than one month duration. After a 5-month follow-up motor improvement was not better in the group receiving additional steroids [31]. Another study compared neurolysis (*n*=21) with neurolysis in combination with perineural corticosteroid injections (*n*=18) for ulnar neuritis of less than six months duration. The injections were administered around the thickened nerve after surgery and two and three weeks later. One year after surgery the mean difference between final and initial nerve function score was 14 for the surgery only group and 21 for the surgery plus steroids group [5]. The third study compared decompressive surgery alone (*n*=59) with surgery plus steroids (*n*=25) given for 3-4 months for sensory impairment of the posterior tibial nerve of varying duration. Satisfactory recovery of nerves with duration of anaesthesia of less than six months was 60% in the surgery group and 83% in the surgery plus steroids group four weeks after surgery [4].

One study compared operated nerves with contralateral non-operated nerves. Prior to surgery all participants had received three months of steroid treatment. The most affected nerves underwent surgical decompression and were compared with the contralateral non-operated nerves one year or more after surgery. Of the more than 100 nerve decompressions four operated nerves had decreased nerve function after one year of follow-up. The other operated nerves had unchanged or improved nerve function one year after surgery. It is unclear how many of the contralateral non-operated nerves improved or deteriorated [35].

After losses to follow-up, another study compared operated nerves (*n*=195) of 95 patients with non-operated nerves of 96 patients, matched for type of leprosy, age and duration of sensory loss but not randomised, on changes in sensation. Participants, in whom no improvement of sensory nerve function was found after a standard steroid treatment (40 mg prednisolone daily for three weeks after which the dosage was reduced by 5 mg per week), were included in the study. Between 27% and 66% of the nerves had definite improvement two years after surgery compared to 7% of the non-operated nerves which improved [36]. Improvement was more likely if the sensory loss had been present for a shorter time. Studies from Carayon et al. favour surgery plus medical treatment above medical treatment alone [1,37,38].

Corticosteroids are the cornerstone of management in acute nerve damage in leprosy, are recommended by the WHO and are widely available. But corticosteroids have some shortcomings. The effects of corticosteroids in the long-term remain uncertain and a considerable proportion of people treated for nerve damage does not benefit from corticosteroid treatment. Long-term therapy may cause serious adverse effects, such as peptic ulcer, cataract, or psychosis. Spontaneous improvement or recovery of nerve function in untreated or placebo treated individuals has been reported and needs more investigation. The limitations of corticosteroids urge the need to find alternative therapeutic approaches [39]. Surgery alone as therapy for treating neuritis is not recommended, but there is discussion about whether the combination of surgery and medical treatment (e.g. steroids) will give better results than medical treatment alone and there is a call for appropriate trials to examine this question [8,9,19].

CONCLUSION

Implications for practice

Evidence from the two randomised controlled trials is insufficient to draw robust conclusions about the effect of decompressive surgery for treating nerve damage in leprosy. Two trials, examining the added benefit of surgery over steroids for neuritis of less than six months duration, did not show significantly better outcomes with steroids plus surgery than steroids alone in the long-term. Adverse effects of decompressive surgery for treating nerve damage in leprosy are not well-documented.

Implications for research

There is a need to identify factors which will predict a favourable response to decompressive surgery or groups of patients or nerves that will be likely to benefit from surgery. Future randomised controlled trials should be well-designed to establish the usefulness and effectiveness of the combination of decompressive surgery and medical treatment compared to medical treatment alone. New trials should pay more attention to non-clinical aspects, such as costs and impact on quality of life, because these are highly relevant indicators for both policy makers and participants.

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CHAPTER 7

Interventions for erythema nodosum leprosum. A Cochrane review

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SUMMARY

Background: Treatment for erythema nodosum leprosum (ENL), an immunological complication of leprosy, is diverse. We undertook a systematic review as it was not clear which treatments were most beneficial.

Methods: We did a systematic search to identify randomised controlled trials (RCTs) comparing treatment with placebo, no treatment or another therapy. Two authors assessed quality and checked data.

Findings: We included 13 studies involving 445 participants. These trials assessed: betamethasone, thalidomide, pentoxifylline, clofazimine, indomethacin and levamisole. The quality of the trials was generally poor and no results could be pooled due to the treatments being so heterogeneous. Treatment with thalidomide showed a significant benefit compared to aspirin (RR 2.43; 95%CI 1.28 to 4.59). Clofazimine treatment was superior to prednisolone (more treatment successes; RR 3.67; 95%CI 1.36 to 9.91) and thalidomide (fewer recurrences; RR 0.08; 95%CI 0.01, 0.56). Minor adverse events were significantly lower in participants on a low dose thalidomide regimen compared to a high dose thalidomide regimen (RR 0.46; 95%CI 0.23 to 0.93). Significantly more minor adverse events were reported in participants taking clofazimine compared with prednisolone (RR 1.92; 95%CI 1.10 to 3.35). None of the studies assessed quality of life or economic outcomes.

Interpretation: There is some evidence of benefit for thalidomide and clofazimine, but generally we did not find clear benefits for interventions in the management of ENL. This does not mean they do not work because the studies were small and poorly reported. Larger studies using clear definitions and internationally recognised scales are urgently required.

INTRODUCTION

This paper is based on a Cochrane review first published in The Cochrane Library 2009, Issue 3 (see http://www.thecochranelibrary.com/ for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

Erythema nodosum leprosum (ENL) or type 2 leprosy reaction is an immune-mediated complication of leprosy, causing inflammation of skin, nerves and other organs, and general malaise [1-3]. ENL only occurs in people with borderline lepromatous (BL) and lepromatous (LL) leprosy. These people have high bacterial loads which increase the risk of ENL. The reported prevalence of ENL among these people is highly variable with high rates (up to 50%) in Asia [4] and lower rates (up to 12%) in Africa [5]. Most people with ENL have multiple acute episodes of ENL or chronic ENL over several years. Few people experience a single acute episode of ENL [4].

Therapies for ENL aim to control the acute inflammation, relieving the pain and preventing further nerve damage or new episodes. The conventional treatment for mild ENL is rest and anti-inflammatory medication. Aspirin is the most commonly used anti-inflammatory drug, but indomethacin, chloroquine and colchicine have been tested as well [2,6]. For severe ENL, prednisolone and clofazimine are most commonly used. Prednisolone usually acts rapidly by controlling the acute inflammation and relieving the pain. The starting dose should be the lowest possible to control ENL and be gradually reduced. The schedule for reducing prednisolone depends on the course of the disease. ENL is often recurrent or chronic and requires high-dose and prolonged courses of prednisolone for the disease to be controlled. This increases the risk of adverse events, such as hypertension or diabetes, and steroid dependency [2,6]. Clofazimine is considered a useful anti-inflammatory drug when corticosteroids are contraindicated or need to be reduced. However, treatment with clofazimine usually takes 4 to 6 weeks to become active and the dose of clofazimine needed to control ENL is higher than the dose used in multi drug therapy (MDT). Disadvantages of continuous high doses of clofazimine are gastrointestinal symptoms (e.g. diarrhoea) and dark discoloration of the skin [2,6,7]. Another drug used to treat ENL is thalidomide. The effectiveness of thalidomide in ENL is primarily due to its action on the proflammatory cytokine TNF but other mechanisms may contribute to its anti-inflammatory effect [8]. The seventh WHO Expert Committee on Leprosy considered thalidomide as an effective treatment of severe ENL, and recommended to restrict thalidomide treatment to male or postmenopausal female patients only. Thalidomide should only be given to women of childbearing age when comprehensive contraceptive precautions can be taken, because its use may cause serious birth defects when taken in early pregnancy [9].

ENL is a serious immunological complication of leprosy. The complex mechanisms underlying ENL are not fully understood yet, which makes treatment difficult. Corticosteroids, clofazimine and thalidomide are the drugs of choice for ENL, but all have drawbacks and the optimal regimen has

not been established. Alternative therapies (e.g. ciclosporin, oral zinc) have been tested, but it is unclear if they are beneficial, or which one is preferable. The role of newer treatments, such as TNF-α antibody treatment, intravenous immunoglobulin, and tenidap, is not known.

METHODS

Search strategy

We searched the Cochrane Skin Group Specialised Register using the following search terms: (leprosy and type and 2) or lepromatous or lepra* or (erythema and nodosum) or 'ENL' or (leprosy and borderline) or leprosum. This search strategy, combined with a search strategy for identifying randomised trials, was adapted to include additional search terms where necessary and was modified to search the Cochrane Central Register of Controlled Trials (*Cochrane Library*, Issue 1, 2009), MEDLINE (from 2003), EMBASE (from 2005), LILACS and AMED (from inception),CINAHL (from 1981) and databases of ongoing trials. All searches were done in March 2009. We checked reference lists of articles. We contacted a person to locate studies from Brazil. There were no language restrictions. Two authors checked the titles and abstracts of all the publications identified to examine which studies were eligible.

Study selection

Studies were eligible if they were randomised controlled trials (RCTs) assessing any therapy for ENL, including systemic corticosteroids, systemic non-steroidal immunomodulatory therapies and diverse therapies. We used the following definition of ENL: 'an inflammatory condition, in which people develop crops of tender erythematous subcutaneous skin lesions'. There may be accompanying neuritis, iritis (inflammation of the iris), arthritis, orchitis (inflammation of the testis), dactylitis (inflammation of the fingers and toes), lymphadenopathy, oedema and fever. The skin signs are obligatory; the nerve and general signs optional [10,11]. The primary outcome measure of interest was the proportion of participants achieving remission of skin lesions. Remission was defined as the absence of new tender erythematous subcutaneous skin lesions at completion of the ENL therapy, as assessed by a clinician. Secondary outcome measures were: the proportion of participants achieving remission of inflammations at other sites, investigator-assessed change in ENL severity, time to next clinical episode of ENL and changes in quality of life. We considered data that had been recorded for four weeks or less from the start of treatment to reflect short-term benefit and these were analysed separately from data that were recorded for more than four weeks from the start of treatment, which we considered to reflect the minimum time period to capture any longer-term benefit. The short-term assessment (one to four weeks) was considered the primary endpoint, because the definite treatment effects should be visible within the first few weeks. The medium-term assessment (between four weeks and six months) was used as a

secondary endpoint. Assessments of more than six months after the start of treatment were considered long-term outcomes.

Methodological quality

The methodological quality of the included studies was based on the following criteria: the method of generation of the randomisation sequence; the method of allocation concealment; who was blinded/not blinded (participants, clinicians, outcome assessors); how many participants were lost to follow-up in each arm and whether participants were analysed in the groups to which they were originally randomised (intention to treat principle); degree of certainty that participants had ENL; baseline comparison for age, sex, duration and severity of ENL; whether outcome measures were clearly described.

Each criterion was assessed as A: adequate, B: unclear or C: inadequate. If one of the criteria was not described in the study, it was labelled 'inadequate'. Two authors independently assessed the included studies for methodological quality.

Data extraction and analysis

One author extracted data regarding methodology and outcome measures from the included studies onto a data extraction form, and a second author checked the data. If there were missing data, the trial authors were contacted. Authors were not blinded to trial author, journal or institution. We used the Cochrane statistical package, Review Manager, for statistical data analysis. Results were expressed as mean differences with 95% confidence intervals (CI) for continuous outcome measures and relative risks (RR) with 95% CI for dichotomous outcomes. We were not able to pool results from studies due to treatments and outcomes being so heterogeneous, and did not perform sensitivity analysis. We did not perform further subgroup analysis due to lack of data on different subgroups (mild versus severe ENL; single acute versus multiple acute versus chronic ENL). Adverse effects that were reported in the included studies were described.

RESULTS

Study selection

We found 269 citations to potentially relevant trials from the electronic searches. Eight potentially eligible studies were found from references of included trials and reviews. Correspondence with authors and other persons and searching of grey literature revealed one potentially relevant trial. We identified 48 possible studies, of which 13 were RCTs. The search of the ongoing trial registers revealed one ongoing trial. We excluded 35 studies of which 21 were not RCTs, two were excluded as they did randomisation by alternation, ten did not have ENL as inclusion criterion, but included participants with lepromatous leprosy in general, one was a duplicate study and one was excluded because it described only intake results and was not completed.

Characteristics of included studies

We included thirteen trials with 445 participants in this review and characteristics of these studies are shown in table 1. Ten studies were published between 1969 and 1985 and three studies between 2002 and 2007. Three trials had a cross-over design and 10 trials had a parallel group design, of which one trial had four parallel groups. The studies involved sample sizes between 9 and 92 participants. Two studies randomised and evaluated ENL reactions of participants. The age range of participants in eight studies was 14 to 69 years; five studies did not report information on the age of the participants. Five studies included both males and females, four studies included only males, and four studies did not report this information. The duration of ENL reactions varied from 0-12.5 years in eight trials, and five trials did not report this information. The severity of reactions ranged from mild to severe and was reported in eight trials.

Interventions

The included studies examined the following interventions.

Systemic corticosteroids:

1. infusion of betamethasone in 5% dextrose versus infusion of 5% dextrose [12]

Systemic non-steroidal immunomodulatory therapies:

– thalidomide versus placebo [13-15]
– thalidomide versus acetylsalicylic acid [16]
– 100 mg thalidomide regimen versus 300 mg thalidomide regimen [17]
– pentoxifylline versus thalidomide [18]
– clofazimine versus placebo [19]
– clofazimine versus thalidomide [20]
– clofazimine versus prednisolone [21]
– indomethacin versus prednisolone [22]
– indomethacin versus chloroquine versus prednisolone versus aspirin [23]
– levamisole versus placebo [24]

Diverse therapies:

– none

Table 1. Characteristics of included studies

Study	Method	Participants	Interventions	Outcomes
Girdhar 2002	parallel group design	Setting: single centre, leprosy centre, India Incl: lepromatous leprosy wit recurrent ENL and on steroids for >6 months, excl: not stated M/F: not stated, age: not stated, duration: not stated, severity: not stated Randomised: 10 participants Evaluable: 9 participants (1 lost to follow-up)	Experimental group (*n*=4): infusion of betamethasone in 5% dextrose daily for 3 days every 4 weeks for 6 months Control group (*n*=5): infusion of 5% dextrose daily for 3 days every 4 weeks for 6 months Other therapy: MDT with 100 mg clofazimine daily for all participants; oral steroids as per need to control ENL for participants in control group	1) Change in severity and frequency of ENL 6 months after end of treatment 2) Steroid requirement 3) Side effects
Pearson 1969	cross over design	Setting: single centre, leprosy centre, Malaysia Incl: moderately severe ENL, Excl: not stated M/F: 11/1, age: not stated, duration: 10 months to 3.5 years, severity: unclear, though title states was moderately severe ENL Randomised: 12 participants Evaluable: 12 participants (1 from group B withdrawn from study after 9 weeks)	Group A (*n*=not stated): thalidomide tablets (100 mg 3 times daily) for 6 weeks, followed by placebo (dose and frequency unknown) for 6 weeks Group B (*n*=not stated): placebo tablets (dose and frequency not stated) for 6 weeks, followed by thalidomide tablets (100 mg 3 times daily) for 6 weeks Other therapy: prednisolone, stibophen and paracetamol in addition to placebo	1) Change in ENL score 2) Steroid requirement 3) Side effects
Waters 1971	cross over design	Setting: single centre, leprosy centre, Malaysia Incl: not stated, but included were participants with lepromatous leprosy and histologically confirmed moderately severe or severe chronic ENL, excl: not stated M/F: 10 M, age: 19-56, duration: 9 months to 3.5 years, severity: moderately severe or severe chronic ENL Randomised and evaluable: 9 participants (16-week trial), 8 participants (24-week trial)	16-week trial (*n*=9) and 24-week trial (*n*=8): Group A (*n*=5 or *n*=3): thalidomide tablets (100 mg 3 times daily) for 4 or 6 weeks, followed by placebo tablets (dose unknown, 3 times daily) for 4 or 6 weeks Group B (*n*=4 or n=5): placebo tablets (dose unknown, 3 times daily) for 4 or 6 weeks, followed by thalidomide tablets (100 mg 3 times daily) for 4 or 6 weeks Other therapy: 100 mg DDS twice weekly, prednisolone or corticotrophin daily, mild analgesics if needed	1) Steroid requirement during trial period 2) ENL score (temperature, severity)

Table 1 Continued

Study	Method	Participants	Interventions	Outcomes
Sheskin 1969	parallel group design	Setting: single centre, hospital/ambulatory, Venezuela Incl: lepromatous leprosy with clearly demonstrable dermatologic, neurologic or other manifestations of ENL reaction, excl: not stated M/F: 37/15, age: 17-58, duration: 3 months to 9 years, severity: not stated Randomised and evaluable: 173 ENL reactions (of 52 participants)	Experimental group (n=85): thalidomide tablets (100 mg 4 times daily if >50 kg, or 6 mg/kg/day if ≤50 kg) for 7 days Control group (n=88): placebo tablets (100 mg 4 times daily if >50 kg, or 6 mg/kg/day if ≤50 kg) for 7 days Other therapy: if on sulfone therapy at admission, sulfone therapy was continued; if receiving steroids or ACTH for prolonged periods at admission, same dosage was continued	1) Total improvement, defined as all dermatologic manifestations in advanced state of remission, no new elements, disappearance of characteristic lepra reaction symptoms after 7 days 2) Side effects
Iyer 1971	parallel group design	Setting: multicentre, 4 centres, India, Mali, Somalia, Spain Incl: clearly demonstrable dermatological signs of acute lepra reactions, excl: severe or life-threatening lepra reactions M/F: 92 M, age: 15-55+, duration: not stated, severity: not stated Randomised and evaluable: 214 ENL reactions (of 92 participants)	Experimental group (*n*=116): thalidomide tablets (100 mg 4 times daily if ≥ 50 kg, or 100 mg 1-3 times daily if < 50 kg) for 7 days Control group (*n*=98): acetylsalicyclic acid tablets (400 mg 4 times daily if ≥ 50 kg, or 400 mg 1-3 times daily if < 50 kg) for 7 days Other therapy: upon admission all drug therapy had to be ceased	1) No further reactions 2) Changes in temperature, skin lesions, blood pressure, pulse rate and blood cell count after 7 days 3) Side effects
Villahermosa 2005	parallel group design	Setting: single centre, leprosy centre, Philippines Incl: lepromatous leprosy, ≥ 18 years, acute histologically confirmed episode of ENL consisting of ≥10 skin nodules, with or without systemic symptoms; women only included if evidence of non-childbearing potential, excl: incapacitating ENL (bed ridden), severe neuritis, thalidomide ingestion within 30 days or corticosteroid ingestion within 2 weeks of enrolment M/F: 22 M, age: 18-46, duration: 0-3 years, severity: not stated Randomised: 22 participants Evaluable: 19 (3 lost to follow-up)	Group A (*n*=12): thalidomide capsules, 100 mg daily (2x50mg, 4xdummy capsules) in week 1, 50 mg daily (1x50mg, 3xdummy capsules) in week 2-3, 4x dummy capsules daily in week 4-7 Group B (*n*=10): thalidomide capsules, 300 mg daily (6x50mg, 0xdummy capsules) in week 1, 200 mg daily (4x50mg, 0xdummy capsules) in week 2-3, 100 mg daily (2x50mg, 2xdummy capsules) in week 4-5, 50 mg daily (1x50mg, 3xdummy capsules) in week 6-7 Other therapy: acetaminophen for participants with fever during first 72 h of study	1) Resolution of inflamed ENL nodules during initial 7-day treatment 2) Global assessment 3) Re-emergence of skin lesions during taper 4) Week 7 lesion counts 5) Recurrence of lesions after taper 7) Safety and adverse events

Table 1 Continued

Study	Method	Participants	Interventions	Outcomes
Sales 2007	parallel group design	Setting: single centre, leprosy centre, Brasil Incl: MB leposy, males between 18-60 y, females over 49 (postmenopausal), clinical and histopathological ENL, excl: acute neuritis requiring CS, hepatic, renal, mental diseases, diabetes and/or immune-deficiencies related to HIV M/F: 38/6, age: 18-69, duration: not stated, severity: not stated Randomised: 44 participants Evaluable: 44 participants (8 lost to follow-up)	Group A (n=24): pentoxifylline (1.2 g daily) for 30 days Group B (n=20): thalidomide (300 mg daily) for 30 days Other therapy: participants with no improvement after 15 days treatment or with severe adverse effects were removed from study and put on recommended regimen of thalidomide or corticosteroids	1) Improvement at end of 30 days treatment, defined as complete elimination of type 2 reactional skin lesion inflammation, normal body temperature and/or regression of systemic symptoms 2) Side effects
Helmy 1971	cross over design	Setting: single centre, leprosy centre, Malaysia Incl: not stated, though included were lepromatous or indefinite leprosy with moderately severe ENL, excl: not stated M/F: 10/5, age: 17-67, duration: 6 months to 2 years, severity: moderately severe ENL Randomised: 15 participants Evaluable: 10 participants (5 lost to follow-up)	Group A (*n*=3): clofazimine capsules (100 mg 3 times daily) in week 1-4, followed by placebo capsules (dose unknown, 3 times daily) in week 5-8. Group B (*n*=7): placebo capsules (100 mg 3 times daily) in week 1-4, followed by clofazimine capsules (dose unknown, 3 times daily) in week 5-8. Other therapy: dapsone (100 mg 2 times daily); stibophen if needed; paracetamol issued twice weekly to be taken freely	1) Severity score of ENL
Iyer 1976	parallel group design	Setting: single centre, India Incl: male, lepromatous leprosy and prone to recurrent reactive episodes, excl: not stated M/F: 72 M, age: 15-54, duration: <6 months to >4 years, severity: moderate, severe Randomised: unclear, states “72 participants available for analysis” Evaluable: 72 participants	Experimental group (*n*=36): clofazimine (100 mg 3 times daily) for 8 weeks, clofazimine (100 mg once a day) + dapsone (10 mg/kg/week) for 52 weeks Control group (n=36): thalidomide (100 mg 3 times daily) for 8 weeks, thalidomide (25-50 mg once a day) + dapsone (10 mg/kg/week) for 52 weeks Other therapy: dapsone (10 mg/kg/week) for 52 weeks	1) Time to control reaction 2) Maintenance of anti-reaction effect after therapy

Table 1 Continued

Study	Method	Participants	Interventions	Outcomes
Karat 1970	parallel group design	Setting: single centre, leprosy centre, India Incl: history of ≥3 severe reactions and with severe current reaction which could not be controlled by antimony, aspirin or chloroquine, excl: peptic ulcer, intercurrent acute infections, TB or malignant lesions M/F: not stated, age: not stated, duration: 4-150 months, severity: severe Randomised and evaluable: 24 participants	Experimental group (*n*=12): clofazimine (100 mg 3 times daily) for 12 weeks Control group (*n*=12): prednisolone (10 mg 3 times daily) week 1, (10 mg 2 times daily) week 2, (5 mg 3 times daily) week 3, (10 mg 2 times daily) week 4, (5 mg once daily) week 5-12 Other therapy: none	1) Treatment success at end of 12 weeks, defined as body temp < 37.2ºC, no new ENL lesions, no pain in peripheral nerve, no progression of neurological deficit, and iritis quiescent in 2 weeks from starting treatment 2) Recurrence of reaction during trial 3) Side effects
Ing 1969	parallel group design	Setting: single centre, Singapore Incl: Lepromatous leprosy and ENL (mild, moderate or severe), excl: not stated M/F: not stated, age: not stated, duration: not stated, severity: 15 mild, 9 moderate, 6 severe Randomised: 30 participants Evaluable: 30 participants, though one participants did not complete 4-week treatment	Experimental group (n=16): indomethacin (25 mg 3 times daily) for 1 month Control group (*n*=14): prednisolone (5 mg 3 times daily) for 1 month Other therapy: anti-leprosy drugs were given during 4-week trial period, but no additional analgesics	1) Improvement after 4 weeks (e.g. mean change in pain relief, subsidence of lesions) 2) Side effects

Table 1 Continued

Study	Method	Participants	Interventions	Outcomes
Karat 1969	parallel group design	Setting: single centre, leprosy centre, India Incl: lepromatous leprosy with ENL, >12 years, excl: history or radiological evidence of peptic ulcer, diabetes, TB, hypertension, severe intercurrent infection, acute peripheral nerve paralysis, medical conditions requiring use of other anti-leprosy drugs M/F: not stated, age: not stated, duration: not stated, severity: 28 mild, 22 severe Randomised and evaluable: 50 participants	Group 1 (*n*=11): indomethacin orally (50 mg 3 times daily) in wk 1-2, (25 mg 3 times daily) in week 3, (25 mg once a day) maintenance Group 2 (*n*=12): chloroquine orally (250 mg 3 times daily) in wk 1-2, (250 mg 2 times daily) in week 3, (250 mg once a day) maintenance Group 3 (*n*=13): prednisolone orally (5 mg 3 times daily) in wk 1-2, (5 mg 2 times daily) in week 3, (5 mg once a day) maintenance Group 4 (*n*=14): aspirin orally (1 g 3 times daily) in wk 1-2, (1 g 2 times daily) in week 3, (500 mg 2 times daily) maintenance Other therapy: anti-leprosy drugs were stopped on admission; sedation with phenobarbitone or chlorpromazine if needed; diuretics only when oedema was progressive and uncontrolled by one of the given drugs	1) Control of reaction 2) recurrence of reaction 3) Side effects
Arora 1985	parallel group design	Setting: single centre, hospital, India Incl: 12 participants with ENL, excl: not stated M/F: 11/1, age: 14-55, duration: 0-7 years, severity: severe Persons analysed: 269 (a: 88, b: 91, c: 90). Randomised and evaluable: 12 participants	Experimental group (*n*=5): levamisole capsules (150 mg daily) on 3 consecutive days repeating every fortnight for 3 months Control group (*n*=7): placebo capsules (dose unknown, daily) on 3 consecutive days repeating every fortnight for 3 months Other therapy: iron for anaemic participants	1) Improvement, defined as complete recovery from reaction, after 3 months

Outcome measures

The outcomes remission of skin lesions and remission of inflammation at other sites were not explicitly reported in any of the trials. Seven trials used different grading scales or scores to assess ENL severity. The secondary outcome of time to next clinical episode was not reported in any of the trials. None of the studies measured changes in quality of life or economic outcomes. Adverse effects were not reported in three trials.

Six trials recorded data only for four weeks or less from the start of treatment, reflecting short-term benefit. Three trials had the outcome assessment at medium term, ranging from four weeks to six months from the start of treatment. One trial assessed long-term benefit, more than six months after treatment. One trial assessed both on short-term and medium-term, and one trial both on medium-term and long-term. The timing of outcome assessment was unclear in one trial.

Methodological quality

The methodological quality of the trials was generally poor. The results of the assessment of methodological quality are shown in Table 2. None of the trials was clear as to how randomisation lists were generated. Concealment of allocation was considered adequate in two trials which had the medication pre-prepared by a drug company [16,17].

Blinding of outcome assessment was attempted for most of the trials, but none of the studies clearly described who (the participants, clinicians and outcome assessors) was blinded.

Information about incomplete outcome data was generally not reported and participant losses ranged between 0 and 33%. Seven trials did not report information on incomplete outcome data, but if accepting no mention in the text and no signs of attrition in tables, as a 100% follow-up, all of these trials had a follow-up rate of 100%. Six trials reported missing data and two performed intention to treat analysis.

Six trials did not perform a statistical analysis, but only described the results. One study [22] reported in the summary that “indomethacin is effective in treating only mild and moderate cases of ENL”. The summary of one study [14] concluded that “nine of the ten participants showed a very significant improvement”. Another study [13] summarised that “thalidomide was superior to a placebo”. None of these studies provided sufficient evidence (e.g. significant test values) to support these claims.

Table 2. Assessment of methodological quality

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other bias[1]
Girdhar 2002	unclear	unclear	unclear	unclear	yes	unclear
Pearson 1969	unclear	unclear	unclear	yes	no	unclear
Waters 1971	unclear	unclear	unclear	unclear	no	unclear
Sheskin 1969	unclear	unclear	unclear	unclear	yes	unclear
Iyer 1971	unclear	yes	unclear	unclear	unclear	unclear
Villahermosa 2005	unclear	yes	unclear	no	yes	unclear
Sales 2007	unclear	unclear	unclear	yes	yes	unclear
Helmy 1971	unclear	unclear	unclear	no	unclear	unclear
Iyer 1976	unclear	unclear	no	unclear	unclear	unclear
Karat 1970	unclear	unclear	unclear	unclear	yes	yes
Ing 1969	unclear	unclear	unclear	unclear	no	unclear
Karat 1969	unclear	unclear	unclear	unclear	yes	unclear
Arora 1985	unclear	unclear	unclear	unclear	yes	unclear

[1] certainty of diagnosis, baseline comparison, explicit outcomes

Five studies specified erythema nodosum leprosum (ENL) in their inclusion criteria. Most other studies did not define ENL, but did mention it under the inclusion criteria. Five studies did not provide data for baseline comparison and seven studies were not clear as to whether groups were similar at baseline. Six studies did not clearly describe outcome measures.

Effects of interventions

Subgroup analysis was not performed as there were no appropriate studies to pool. Of the 13 studies included, none compared the same interventions or had comparable outcomes. We did not find any trials assessing diverse therapies for ENL. Quality of life and economic outcomes were not included in any of the trials.

PRIMARY OUTCOME MEASURE

(a) The proportion of participants achieving remission of skin lesions

None of the studies reported the absence of new skin lesions at the end of therapy. Two studies had outcome measures that were considered to reflect our primary outcome measure, Karat et al. [21] reported treatment success, including absence of new ENL lesions and Sheskin et al. [15] reported improvement, including absence of new ENL lesions, but did not provide separate data of the first randomised treatment regimen for comparison. Five studies reporting differing definitions of remission of skin lesions. One study reported the number of participants with no further

reaction after the first treatment regimen, implying absence of new ENL skin lesions [16]. Three studies reported the resolution of existing skin lesions [17,18,22].

Systemic corticosteroids

Remission of skin lesions was not reported for any systemic corticosteroid interventions.

Systemic non-steroidal immunomodulatory therapies

Short-term:

Significantly more participants who received thalidomide treatment had no further reaction after seven days, requiring a second treatment regimen, compared to those receiving acetylsalicylic acid (aspirin) treatment (RR 2.43; 95% CI 1.28 to 4.59; *n*=92) [16]. No significant difference in resolution of existing inflamed ENL nodules was found between the 100 mg thalidomide regimen and the 300 mg thalidomide regimen after seven days (RR 1.33; 95% CI 0.64 to 2.79; *n*=22) [17]. No significant difference in the resolution of existing inflamed ENL skin nodules was observed between pentoxifylline and thalidomide after 30 days of treatment (RR 1.05; 95% CI 0.74 to 1.49; *n*=25) [18]. No significant difference in complete subsidence of existing ENL lesions was found between indomethacin and prednisolone after four weeks (RR 2.33; 95% CI 0.76 to 7.13; *n*=30) [22].

Medium-term:

One participant, who had received the 300 mg thalidomide regimen, had a successful taper, defined as a complete response after seven days and lack of new acutely inflamed lesions during the six week taper and for at least two months after stopping thalidomide [17]. Significant more treatment successes were observed in the clofazimine group compared to the prednisolone group at the end of 12 weeks of treatment (RR 3.67; 95% CI 1.36 to 9.91; *n*=24) [21].

SECONDARY OUTCOME MEASURES

(a) The proportion of participants achieving remission of inflammations at other sites

Remission of inflammations at other sites was not reported in any of the studies, or inadequately [16] (no separate data of the first randomised treatment regimen).

(b) Investigator-assessed change in ENL severity

One study used a global assessment score to assess for changes in ENL symptoms (anorexia, arthralgias, chills, malaise, neuritis, orchitis and fever) [17]. One study used a grading scale (0-3) to assess changes in ENL severity, with higher grades indicating more severe ENL [24]. One study [13] used an ENL severity score, but did not provide individual participant data or means and standard deviations for comparison. Two studies assessed change in ENL severity using different

scoring methods, but provided only sum scores of the weekly scores over the four weeks trial period [14,19]. One study assessed the frequency and severity of ENL, but did not provide data or significant test values for comparison [12]. One study reported control of reaction, but it was unclear how control was defined [23]. It was unclear whether any of the scales used had been formally validated.

Systemic corticosteroids

Change in ENL severity was not reported for any systemic corticosteroid interventions.

Systemic non-steroidal immunomodulatory therapies

Short-term:

No significant difference in improvement (becoming asymptomatic) was found between the 100 thalidomide regimen and the 300 mg thalidomide regimen after seven days of treatment (RR 1.67; 95%CI 0.85 to 3.26; *n*=22) [17].

Medium-term:

No significant difference in improvement (change from grade 3 to grade 1 or 0) was observed between levamisole and placebo after three months (RR 0.95; 95%CI 0.36 to 2.49; *n*=12) [24]. No significant difference in control of reaction was found between indomethacin and chloroquine (RR 0.95; 95% CI 0.52 to 1.74; *n*=23), prednisolone (RR 0.65; 95% CI 0.41 to 1.02; *n*=24) and aspirin (RR 0.89; 95% CI 0.51 to 1.55; *n*=25) respectively. The duration of the trial and timing of outcome assessment was unclear; the paper stated both a trial period of 90 days and of 12 months [23].

(c) Time to next clinical episode of ENL

Time to next clinical episode of ENL was not reported in any of the studies. Four studies reporting differing definitions of time to next clinical episode of ENL. One study reported recurrence of new lesions by week 7 in participants who had achieved remission of existing ENL skin lesions at the end of the first week [17]. One study reported relapse of ENL within 52 weeks after treatment [20]. Two studies reported recurrence of ENL by the end of the trial period in participants whose initial reaction was controlled in this same period [21,23].

Systemic corticosteroids

Time to next clinical episode of ENL was not reported for any systemic corticosteroid interventions.

Systemic non-steroidal immunomodulatory therapies

Medium-term:

No significant difference in recurrence of new lesions after seven weeks was observed between the 100 mg thalidomide regimen and the 300 mg thalidomide regimen (RR 3.75; 95% CI 0.62 to

22.64; *n*=13) [17]. No significant difference in recurrence of ENL was found between clofazimine and prednisolone at the end of 12 weeks (RR 0.14; 95% CI 0.02 to 1.04; *n*=14) [21].

Long-term:

Results showed significantly less participants with relapse of ENL in the clofazimine group compared to the thalidomide group within 52 weeks after treatment (RR 0.08; 95% CI 0.01 to 0.56; n=72) [20]. No significant difference in recurrence of ENL was observed between indomethacin and chloroquine (RR 1.14; 95% CI 0.44 to 2.94; *n*=15), prednisolone (RR 0.83; 95% CI 0.40 to 1.72; *n*=20) or aspirin (RR 0.82; 95% CI 0.38 to 1.74; *n*=17) respectively at the end of the trial period (90 days or 12 months) [23].

(d) Changes in quality of life

None of the trials reported changes in quality of life.

Adverse events

Three trials did not report on adverse events [19,20,24]. The other trials did provide information about adverse events, but often the number of participants with any adverse events in both groups was unclear.

Systemic corticosteroids

Minor adverse events not requiring withdrawal from treatment (swelling of the face, 'buffalo hump', striae distensae and acne) were more often reported in participants who received intravenous dextrose alone and oral steroids per their need to control ENL (control group) compared to those who received intravenous betamethosane in 5% dextrose, but the number of participants with adverse events in each group was not given [12].

Systemic non-steroidal immunomodulatory therapies

Withdrawals from thalidomide treatment were caused by intestinal obstruction (1/12 participants) [13], and worsening of ENL symptoms (3/22 participants) [17]. Minor adverse events not requiring withdrawal from thalidomide treatment (e.g. mild dermatitis, constipation, nausea, drowsiness, headache, insomnia, dizziness, dryness) were reported, but data for comparison was unclear or lacking [13-16,18]. Significantly less participants in the 100 mg thalidomide regimen group reported any mild to moderate adverse events compared to those in the 300 mg thalidomide regimen group during the 7-week regimen (RR 0.46; 95%CI 0.23 to 0.93; *n*=22) [17]. Withdrawals from pentoxifylline were due to gastrointestinal intolerance to the drug (1/24 participants) and fever and continuing lesion inflammation (3/24 participants). Adverse events not requiring withdrawal from pentoxifylline treatment (e.g. gastrointestinal complaints, nausea) were reported in 2/24 participants [18]. Significantly more participants who received clofazimine had minor adverse

events compared to those who received prednisolone (RR 1.92; 95%CI 1.10 to 3.35; n=24). In the clofazimine group all participants had red/black pigmentation. No withdrawals from either clofazimine or prednisolone treatment were reported [21]. Withdrawal from indomethacin treatment was due to deterioration of ENL (1/16 participants). Minor adverse events (e.g. nausea, dizziness, insomnia) were more frequently reported in participants who received indomethacin (9 events) compared to those who received prednisolone (1 event) [22]. No significant differences in minor adverse events (e.g. abdominal pain, nausea, headache) were observed between indomethacin and chloroquine (RR 1.09; 95% CI 0.57 to 2.10; *n*=23), prednisolone (RR 0.92; 95% CI 0.52 to 1.63; *n*=24) and aspirin (RR 2.23; 95% CI 0.87 to 5.71; *n*=25) respectively [23].

DISCUSSION

Summary of main results

There are no good controlled trial data on the optimum treatment for controlling the acute phase of ENL. Our review included 13 randomised controlled trials involving 445 participants, and assessed the effects of betamethasone, thalidomide, pentoxifylline, clofazimine, indomethacin and levamisole in the management of ENL. One trial showed thalidomide treatment to be superior to acetylsalicylic acid treatment (less new reactions requiring further treatment) in the short-term control of ENL [16]. Two trials showed significant longer-term benefits of clofazimine treatment compared to thalidomide (fewer recurrences) or prednisolone (more treatment successes) respectively [20,21]. Mild to moderate adverse events were significantly higher in participants taking a 300 mg versus 100 mg dose of thalidomide [17] and in participants taking clofazimine compared with prednisolone [21].

The results should be considered with caution, due to methodological shortcomings. Data extraction of the study of Iyer et al. was limited to the results of the first randomised treatment regimen to avoid having more than one outcome per participant in the analysis [16]. In another study participants continued on a maintenance dose of either 100 mg clofazimine or 50 mg thalidomide daily during the year after therapy. The study found significantly less recurrences of ENL in the group who received clofazimine therapy and this effect may be due to the persistance of clofazimine in the body over a longer period of time [20]. Karat et al. tapered the dose of prednisolone (starting at 30 mg daily and tapered off to 5 mg daily), while the dose of clofazimine (300 mg daily) remained the same during the 12-week treatment [21].

Quality of the evidence

The quality of trials was generally poor, especially in studies published more than twenty years ago, due to the lack of clear reporting of methods, data and the allocation process. Most of the studies were too small (10 to 92 participants) to identify important differences even if they existed.

Three studies had a cross-over design which is associated with increased risk of bias [13,14,19]. We therefore considered only results of the first phase treatment if these data were available. Two studies used more than one outcome of individual participants in the analysis [15,16]. This may have led to an over-estimate of the effect because the within-patient variance between outcomes of the same person may be smaller than the between-patient variance of outcomes between individuals. We used only data of the first randomised treatment to overcome this concern and these were only available for the trial of Iyer et al. [16]. Most of the trials reported co-medication, which may have diluted the effect of the intervention tested in the studies. Most of the studies were not clear as to how allocation sequences were generated or how allocation was concealed. Blinding, especially of the outcome assessor, was not described at all or unclear. Trials assessing clofazimine were unblinded the moment skin discoloration appeared. This might have biased the outcome assessments. Six studies reported incomplete outcome data, but only two of those performed an intention to treat analysis. Baseline data were poorly reported and absent in five studies. Adverse effects were often reported inadequately, limiting comparisons between experimental and control groups.

CONCLUSION

Implications for practice

There is some evidence of benefit for thalidomide and clofazimine, but generally we found insufficient evidence to make any firm recommendations on the use of any of the interventions tested for management of ENL and included in this review. This does not mean they do not work, because the studies were generally of poor quality and small-sized.

Treatment with thalidomide showed a significant benefit compared to acetylsalicylic acid (aspirin). Clofazimine treatment was superior to prednisolone and thalidomide. Current guidelines for the management of ENL are given by bodies such as the World Health Organization (WHO) and the International Federation of Anti-Leprosy Associations (ILEP), but these guidelines are not supported by evidence from randomised controlled trials and are developed from practice.

Most of the studies reported adverse effects of treatment. Mild to moderate adverse events were significantly higher in participants taking a 300 mg versus 100 mg dose of thalidomide and in participants taking clofazimine compared with prednisolone. Only in a few instances withdrawal from treatment was required, but it was not always clear whether this was due to treatment or for another reason. Adverse effects of commonly used drugs, such as prednisolone, clofazimine and thalidomide are well-documented and should be kept in mind when prescribing drugs for ENL.

Implications for research

The thirteen trials included in this review were generally of poor methodological quality and have mostly been of short duration. A wide range of interventions were assessed, one trial evaluated betamethasone, five trials thalidomide, one trial pentoxifylline, three trials clofazimine, two trials indomethacin and one trial levamisole.

It was often unclear what the duration and severity of ENL was before the starting of treatment. Future studies should have clearer case definitions for ENL and we recommend that different durations of ENL (single acute episode, multiple acute episode or chronic) and different severity of ENL (mild or severe) be distinguished, as such subgroups may need different management of ENL. Erythema nodosum leprosum is a complicated disease known for its unpredictability, its variable severity and duration, and its often chronic and recurrent nature. Although most agents may work similarly for controlling the acute symptoms of ENL, prevention of recurrences is far more difficult. There is a need for good quality studies which follow the current standards for design and reporting of randomised controlled trials, and for large multi-centre studies to ensure that enough participants are enrolled.

None of the studies investigated whether the interventions improved quality of life of participants and only a few examined the long-term effects of interventions. There is a need for clearly defined outcome measures, both at short-term and longer-term. We would recommend that future studies include outcomes, such as absence of new tender erythematous subcutaneous skin lesions at completion of the ENL therapy, disappearance of ENL associated inflammation at other sites than the skin (such as iritis and arthritis) at completion of the ENL therapy, time to next clinical episode of ENL after completion of treatment, and quality of life measures.

It is recommended that internationally recognised and validated severity scales be developed so that results from different countries can be compared.

A trial comparing directly prednisolone and thalidomide has never been done, and is urgently needed.

Future studies should aim to assess the efficacy, safety and optimal regimens of prednisolone and thalidomide for severe ENL and clofazimine for mild ENL as well as other potentially beneficial therapies.

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CHAPTER 8

Evaluation of activity limitation and social participation, and the effects of reconstructive surgery in people with disability due to leprosy: a prospective cohort study

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CHAPTER 9

Cost-effectiveness of interventions to prevent disability in leprosy: a systematic review

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SUMMARY

Background: Prevention of disability (POD) is one of the key objectives of leprosy programmes. Recently, coverage and access have been identified as the priority issues in POD. Assessing the cost-effectiveness of POD interventions is highly relevant to understanding the barriers and opportunities to achieving universal coverage and access with limited resources. The purpose of this study was to systematically review the quality of existing cost-effectiveness evidence and discuss implications for future research and strategies to prevent disability in leprosy and other disabling conditions.

Methods: We searched electronic databases (NHS EED, MEDLINE, EMBASE, and LILACS) and databases of ongoing trials (www.controlled-trials.com/mrct/, www.who.int/trialsearch). We checked reference lists and contacted experts for further relevant studies. We included studies that reported both cost and effectiveness outcomes of two or more alternative interventions to prevent disability in leprosy. We assessed the quality of the identified studies using a standard checklist for critical appraisal of economic evaluations of health care programmes.

Findings: We found 66 citations to potentially relevant studies and three met our criteria. Two were randomised controlled trials (footwear, management of neuritis) and one was a generic model-based study (cost per DALY). Generally, the studies were small in size, reported inadequately all relevant costs, uncertainties in estimates, and issues of concern and were based on limited data sources. No cost-effectiveness data on self-care, which is a key strategy in POD, was found.

Interpretation: Evidence for cost-effectiveness of POD interventions for leprosy is scarce. High quality research is needed to identify POD interventions that offer value for money where resources are very scarce, and to develop strategies aimed at available, affordable and sustainable quality POD services for leprosy. The findings are relevant for other chronically disabling conditions, such as lymphatic filariasis, Buruli ulcer and diabetes in developing countries.

INTRODUCTION

Leprosy is a leading cause of permanent disability among communicable diseases. An estimated three million people live with disability due to leprosy [1] and it is expected that up to one million people will continue to suffer from disability in the next decades [2]. The International Classification of Functioning, Disability and Health (ICF) defines disability as 'an umbrella term for impairments, activity limitations and participation restrictions' [3]. This definition goes beyond the concept of considering disability in medical terms only, and recognises the social context of disability. More than most other diseases, leprosy has a very negative image. People with visible disability fear stigmatization and discrimination, and experience serious psychosocial and economic problems [4-6]. One of the main components of leprosy programmes and research has been prevention of disability (POD). Interventions include: early detection and treatment of reactions and nerve damage, self-care interventions, health education, footwear programmes, and reconstructive surgery. More recently, the need for clear and sound guidance for leprosy control activities resulted in the organization of a technical forum by the International Leprosy Association (ILA). Their report, published in 2002, reviewed the existing literature for the effectiveness of important issues related to leprosy control, but did not address cost-effectiveness [7]. In 2006, a Consensus Development Conference on prevention of disability in chronically disabling conditions, such as leprosy, lymphatic filariasis, Buruli ulcer and diabetes was held. The main research theme of the conference was how to achieve universal coverage of essential POD interventions. One of the conclusions was that priority should be given to research that addresses issues of coverage and access [8].

In developing or low-income countries, cost-effective interventions often do not reach many of those who need them most. Achieving universal coverage usually means 'going to scale', defined as 'a policy that builds on one or more interventions with known effectiveness and combines them into a programme delivery strategy designed to reach high, sustained, and equitable coverage, at adequate levels of quality, in all who need the interventions'. It assumes that the chosen interventions for scaling up are known to be feasible, affordable, and effective for implementation in the specific setting [9].

Evidence for the effectiveness of POD interventions in leprosy is limited. Recently, two systematic reviews have been published. One review assessed the effects of corticosteroids for treating nerve damage in leprosy [10] but did not find evidence from randomised controlled trials for a significant long-term effect of steroid therapy in improving either mild sensory nerve function impairment [11] or longstanding nerve function impairment [12].

The second review assessing the effects of interventions for skin damage in leprosy [13] found weak evidence favouring topical ketanserin over clioquinol cream or zinc paste [14] and topical phenytoin over saline dressing [15,16] in ulcer healing. No evidence from randomised controlled trials for the effectiveness of self-care or educational interventions was found. Cost-effectiveness data are even more limited, though the importance of cost-effectiveness analysis has been recognised. The ILA

technical forum included a research question about which methods are most cost-effective, but did not answer this question in their report [7]. The consensus statement on POD mentioned that it would be more cost-effective to combine POD strategies and interventions for several related chronically disabling conditions in leprosy-endemic countries, and recommended further research on cost-effective methods to promote self-care and the use of appropriate footwear [8].
We assessed the existing literature on cost-effectiveness of POD interventions in leprosy as it was not clear which interventions were most cost-effective, using a standard checklist for economic evaluations and discussed the findings in the light of availability, affordability, and sustainability of POD interventions for leprosy and other chronically disabling conditions in developing countries.

METHODS

Searching

In November 2008, a systematic search was done. We searched the NHS EED database (from 1994) using the search term: leprosy. We searched MEDLINE (from 1966), EMBASE (from 1980), and LILACS (from 1982), using the strategy in table 1. We searched databases of ongoing trials (www.controlled-trials.com/mrct/, www.who.int/trialsearch), we checked reference lists for any additional relevant studies, and we contacted experts in leprosy for ongoing studies or unpublished data. There were no language restrictions when we searched for publications.

Selection

We included studies that met the following criteria:

- assessing interventions to prevent disability in leprosy and
- comparing two or more competing alternatives and
- reporting both cost and effectiveness of the interventions compared
- There were no restrictions on the type of study design when we searched for publications.

Validity assessment

We assessed the quality of the studies, using a check-list from Drummond al. [17], consisting of ten essential questions, for critically appraising studies of economic evaluation of health care programmes (see table 2). With respect to question 10 (did the presentation and discussion of study results include all issues of concern to users), we focussed on availability, affordability, and sustainability. Availability includes issues of coverage and access, affordability means that each of the parties involved is able and willing to pay for a given health care programme or intervention, and sustainability refers to long-term strategies for sustaining health care programmes.

Table 1. Search strategy for identifying economic evaluations of interventions to prevent disability in leprosy

#	Term	Field
1	economics	MeSH Subheading
2	economic evaluation	title or abstract
3	cost-benefit analysis	title or abstract
4	cost-effectiveness analysis	title or abstract
5	cost-effective	title or abstract
6	cost-utility analysis	title or abstract
7	cost	title or abstract
8	costs	title or abstract
9	or/1-8	
10	leprosy	title or abstract
11	hansen's disease	title or abstract
12	hansen disease	title or abstract
13	or/10-12	
14	disability	title or abstract
15	disabled	title or abstract
16	deformity	title or abstract
17	deformed	title or abstract
18	impairment	title or abstract
19	impaired	title or abstract
20	neuritis	title or abstract
21	nerve damage	title or abstract
22	nerve function impairment	title or abstract
23	reaction	title or abstract
24	reactions	title or abstract
25	ulcer	title or abstract
26	eye damage	title or abstract
27	visual impairment	title or abstract
28	blindness	title or abstract
29	footwear	title or abstract
30	self-care	title or abstract
31	surgery	title or abstract
32	or/14-31	
33	9 and 13 and 32	

Data abstraction and study characteristics

One author (NvV) extracted the relevant data (e.g. type of study design, interventions, outcome measures) from the eligible studies and a second author (PMN) checked the data. The authors discussed discrepancies between themselves. Missing data were obtained from study authors where possible. The authors were not blinded to the names of study authors, journal or institutions.

Table 2. Check-list for assessing economic evaluations

1	Was a well-defined question posed in answerable form?
2	Was a comprehensive description of the competing alternatives given?
3	Was the effectiveness of the programmes or services established?
4	Were all the important and relevant costs and consequences for each alternative identified?
5	Were costs and consequences measured accurately in appropriate physical units?
6	Were costs and consequences valued credibly?
7	Were costs and consequences adjusted for differential timing?
8	Was an incremental analysis of costs and consequences of alternatives performed?
9	Was allowance made for uncertainty in the estimates of costs and consequences?
10	Did the presentation and discussion of study results include all issues of concern to users?

From: Drummond al. [17]

Quantitative data synthesis

For studies with a similar type of POD intervention, we planned to calculate standardised estimates of the cost per disability-adjusted life-year (DALY). Where it was not possible to pool data, we summarised the cost-effectiveness data for each study.

RESULTS

Flowchart

The electronic searches found 62 citations to potentially relevant studies. Two further potentially eligible studies were found from reference lists of included studies and reviews. Correspondence with experts in leprosy and searching of grey literature revealed another two potentially relevant studies. We identified seven possible studies of economic evaluation. The search of the ongoing trial registers did not reveal any ongoing trials. We excluded four studies. One study was a review paper describing only costs of different components of a global leprosy elimination programme [18]. The second study modelled the productivity gains if deformity would be eliminated [19]. The third study assessed only the cost of offering disability care either through community volunteers or leprosy workers at the clinic [20]. The fourth study was an unpublished report describing guidelines for doing a systematic cost analysis in leprosy control programmes [21]. Figure 1 shows the selection process of the studies.

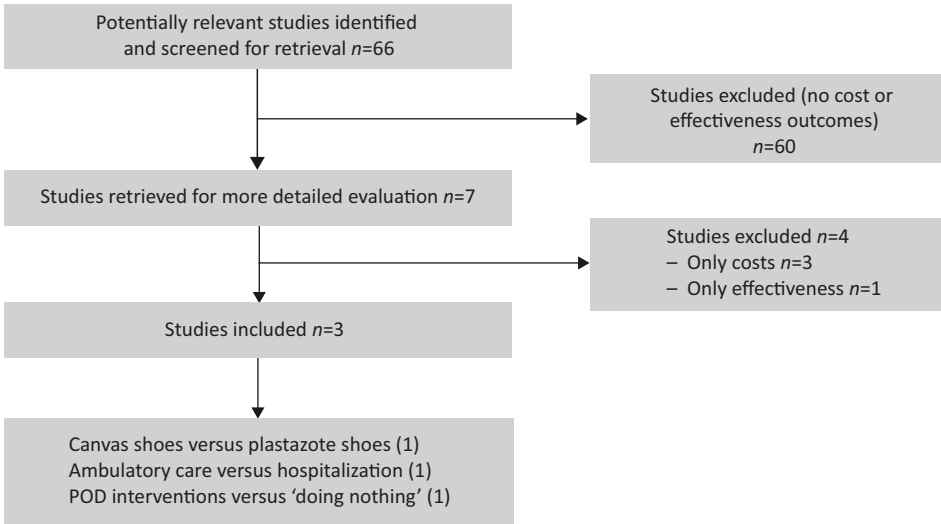

Figure 1. Flowchart of selection process

Study characteristics

We included three studies. Two studies were small, single-centre randomised controlled trials. One trial (Seboka 1996) assessed the cost-effectiveness of canvas shoes compared to plastazote shoes in terms of cost per ulcer healed or prevented [22]. The other trial (Ravi 2004) compared the cost of ambulatory care to hospitalisation in the management of neuritis and used the number of days needed to return to work as primary outcome of effectiveness [23]. The third study (Remme 2006) reviewed the effectiveness of interventions and calculated cost of existing interventions per DALY averted [24]. It was published in the second edition of the World Bank publication 'Disease Control Priorities in Developing Countries' [25]. Table 3 summarises the general characteristics of the three studies.

Validity assessment

For a critical appraisal of the studies, we answered all ten questions of the standard checklist [17] for each of the studies identified. The results of the critical assessment are summarised in table 4.

1. WAS A WELL-DEFINED QUESTION POSED IN ANSWERABLE FORM?

The three studies did not state explicitly the viewpoint for the analysis (e.g. a specific provider or providing institution, the patient or groups of patients, a third-party payer, or society). Seboka 1996 implicitly referred to third-party payers (donors) with respect to long-term costs. Ravi 2004 estimated costs incurred by the health sector and the patient, and indirect costs due to lost working days, implying a societal perspective for the analysis. Remme 2006 included only direct costs to the health system of delivering interventions.

Table 3. General characteristics of included studie

Study ID	Seboka 1996	Ravi 2004	Remme 2006
Design	Randomised controlled trial	Randomised controlled trial	Model-based study
Randomisation procedure	Randomisation by day of attendance to clinic	Randomisation by computerized random numbers table	Not applicable
Setting	Foot-care clinic near Sheshemane, Ethiopia	Skin and leprosy department of tertiary level hospital in Tamilnadu, India	Not applicable
Time of study	November 1994 to November 1995	October 1999 to March 2001	Not applicable
Number of patients	70	26	Not applicable
Inclusion	Leprosy patients with deformed and anaesthetic feet	Leprosy patients with neuritis < 6 month duration due to type 1 or type 2 reaction	Not applicable
Male/female	28/40 (2 unknown)	23/3	Not applicable
Mean age (range)	Not described (unclear)	31 (15-49) (exp)[1]; 41 (19-60) (cont)[2]	Not applicable
Lost to follow-up	2 (cont)[2]	4 (2 exp, 2 cont)[1 2]	Not applicable
Interventions	Experimental group (*n*=40): canvas shoes	Experimental group (n=13): ambulatory care: education and steroid therapy (mean duration 4.3 months)	Treatment for reactions and ulcers, footwear and self-care education, reconstructive surgery
	Control group (n=30): plastazote shoes	Control group (n=13): hospitalisation for 2 weeks plus steroid therapy (mean duration 4.5 months)	Comparing total cost and benefits of existing interventions, starting from zero
Outcomes	Healing of existing ulcers	Number of days needed to return to work after stipulated period of admission or rest (2 weeks)	Cost per DALY averted
	Prevention of ulceration	Mean cost per patient	Average cost of POD per new leprosy case with disability
	Acceptability of shoes	Improvement in quality of life score	
	Durability of shoes	Improvement in sensory and motor score	
	Cost-effectiveness of shoes		
Timing of outcome assessment	One year after start from study	At the end of steroid therapy	Not applicable

[1] exp: experimental group; [2] cont: control group

2. WAS A COMPREHENSIVE DESCRIPTION OF THE COMPETING ALTERNATIVES GIVEN?

Seboka 1996 compared two types of protective footwear, canvas shoes and plastazote or moulded shoes. Ravi 2004 assessed neuritis management through either ambulatory care or hospitalisation. Patients in the in-patient group were admitted for two weeks and were monitored in the ward for complications of steroid therapy. Patients receiving ambulatory care were educated regarding the complications of steroids and were advised rest at home for 2 weeks. Remme 2006 reviewed several existing POD interventions, compared to doing nothing.

Table 4. Quality of included studies

	Study ID		
Criteria	Seboka 1996	Ravi 2004	Remme 2006
1) Well-defined question stated?	no [a]	no [a]	no [a]
2) Description of alternatives given?	yes	yes	yes
3) Evidence of effectiveness established?	yes	yes	yes
4) Relevant costs and outcomes identified?	no [b]	not sure [c]	no [d]
5a) Costs measured accurately?	no [e]	yes	no [f]
5b) Outcomes measured accurately?	no	yes	yes
6a) Costs valued credibly?	yes	yes	yes
6b) Outcomes valued credibly?	not applicable [g]	not applicable [g]	not sure [h]
7a) Costs discounted?	not applicable [i]	not sure [j]	yes
7b) Outcomes discounted?	not applicable [i]	not sure [j]	yes
8) Incremental analysis performed?	no	no	no
9) Sensitivity analysis performed?	no	no	no
10a) Issue of availability addressed?	no	no	no
10b) Issue of affordability addressed?	no	no	no
10c) Issue of sustainability addressed?	yes	no	no

[a] no viewpoint for the analysis stated; [b] only cost of shoes included; [c] not sure whether shared costs were taken into account; [d] only direct health care cost included; [e] wholesale price or estimated cost of pair of shoes; [f] estimated costs based on limited published data and expert opinion; [g] outcomes in natural units; [h] disability weights of DALY based on consensus of experts, but not on patient's values or preferences; [i] all costs and consequences occurred within one year; [j] not sure whether discounting was done

3. WAS THE EFFECTIVENESS OF THE PROGRAMMES OR SERVICES ESTABLISHED?

Evidence of effectiveness of footwear and neuritis management came from the trials itself (Seboka 1996 and Ravi 2004 respectively). Remme 2006 reviewed the literature for the effectiveness of POD interventions. Early case detection and treatment were considered as the most effective interventions to prevent disability in leprosy, and self-care as the main strategy to prevent worsening of impairments.

4. WERE ALL THE IMPORTANT AND RELEVANT COSTS AND CONSEQUENCES FOR EACH ALTERNATIVE IDENTIFIED?

Seboka 1996 included only the wholesale price for which the canvas shoes were purchased. Plastazote shoes were provided free-of-charge for the purpose of this study. The cost of organizing and operating the footwear service or the cost to the patient and family for follow-up visits was not measured. Ravi 2004 collected data on different cost categories, covering direct medical costs (e.g. examinations, medication, in-patient care), direct non-medical costs (e.g. transport and food of visitors and patients) and indirect costs (e.g. working days and wages lost), but it was unclear as to whether shared costs were taken into account. Remme 2006 estimated only the direct health care cost of delivering interventions.

Seboka 1996 used programme specific outcome measures of effectiveness (change in ulcer size, the acceptability, usefulness and durability of the footwear), but no generic quality of life outcome. The occurrence of adverse effects was not explicitly addressed, but the study did report that at least one out of five subjects in the plastazote group, who were initially ulcer-free, developed ulcers due to ill-fitting shoes. The primary outcome in Ravi 2004 was the number of days needed to return to work and this was considered a surrogate marker for effectiveness of treatment and well-being of the patient. Secondary outcomes were: mean cost per patient, improvement in nerve function scores and quality of life scores. None of the patients reported any significant adverse effects of steroid therapy. Remme 2006 used a generic outcome measure, the disability-adjusted life years (DALYs) and did not report on adverse effects.

5. WERE COSTS AND CONSEQUENCES MEASURED ACCURATELY IN APPROPRIATE PHYSICAL UNITS?

The costs in Seboka 1996 were straightforward, but inaccurate; the wholesale price or estimated cost of a pair of shoes. Ravi 2004 calculated costs by multiplying the quantities of the resources used and the unit cost of each resource (e.g. cost of each examination, bed and nursing cost, transportation cost). Remme 2006 measured cost as cost of an intervention per patient. Costs were estimated from limited published cost data, programme expenditure data, and expert opinion.

Seboka 1996 measured the primary outcome in natural units; the number of ulcers healed or prevented. It was unclear what scale or score was used to measure acceptability and usefulness of the footwear. Ravi 2004 measured the primary outcome, the number of days needed to return to work, from the stipulated period of rest or admission. Improvement in nerve function was measured as a mean score using graded nylon filaments (score per nerve) and the Medical Research Council (MRC) scale (0-5 score per nerve). Quality of life was measured as a mean score using a questionnaire (20 questions, maximum score of 106) derived from the WHO QOL Global pool of questions. Remme 2006 measured the outcome in DALYs.

6. WERE COSTS AND CONSEQUENCES VALUED CREDIBLY?

Seboka 1996 reported the prevailing wholesale price of a pair of canvas shoes in US dollars. Ravi 2004 reported costs in local currency (Indian rupees) based on prevailing prices. Remme 2006 converted cost estimates to US dollars 2000.

Seboka 1996 and Ravi 2004 measured the primary outcome in natural units, which does not require valuation of benefits in money terms. Remme 2006 valued outcomes in DALYs. The disability weights used to value the duration and severity of a particular disease or condition have been criticised, because these were established by expert opinion and consensus [26]. For leprosy, a disability weight of 0.152 was given to disabling leprosy and a weight of 0.000 to a leprosy case without disability [27]. These weights are likely to be underestimated, since they will not adequately capture all the disability resulting from leprosy, such as the major psychosocial impact of leprosy on the lives of leprosy patients, regardless of having disability or not [24].

7. WERE COSTS AND CONSEQUENCES ADJUSTED FOR DIFFERENTIAL TIMING?

Because Seboka 1996 was a one-year trial and all the costs and consequences occurred within a one-year period, no discounting was needed. The trial of Ravi 2004 had a duration of 1.5 years. The study did not report on discounting. In Remme 2006 discounting of costs was done using a 3% rate. The DALY incorporates a constant annual discount rate of 3% for outcomes [28].

8. WAS AN INCREMENTAL ANALYSIS OF COSTS AND CONSEQUENCES OF ALTERNATIVES PERFORMED?

Seboka 1996 and Ravi 2004 did not perform an incremental analysis. Although the canvas shoes and ambulatory care intervention had lower costs and higher effectiveness compared to the plastazote shoes and hospitalisation intervention respectively, no information on a statistically significant difference between the two competing alternatives was given. Remme 2006 calculated the average cost-effectiveness of existing interventions.

9. WAS ALLOWANCE MADE FOR UNCERTAINTY IN THE ESTIMATES OF COSTS AND CONSEQUENCES?

None of the studies performed a sensitivity analysis.

10. DID THE PRESENTATION AND DISCUSSION OF STUDY RESULTS INCLUDE ALL ISSUES OF CONCERN TO USERS?

Availability: none of the studies discussed the issue of coverage and access.

Affordability: none of the studies discussed whether all parties involved would be able and willing to pay for POD programmes.

Sustainability: Seboka 1996 mentioned that the cost of providing footwear to patients for many years may be costly and will require long-term commitment from donors. The other studies did not discuss issues of sustainability.

Quantitative data synthesis

We summarised the cost-effectiveness data for each study, because it was not possible to pool the data for calculating standardised estimates of the cost per disability-adjusted life-year (DALY). Seboka 1996 calculated the cost-effectiveness of canvas shoes compared to plastazote shoes to prevent and heal ulcers in leprosy patients with deformed and anaesthetic feet. The average cost per ulcer healed or prevented over a one-year period was $24.4 and $44.7 respectively. Additional information about the results of the plastazote group was obtained from one of the authors. The average cost per ulcer healed or prevented over a one-year period was at minimum $160 and $373 respectively.

Ravi 2004 calculated costs and effectiveness of ambulatory care compared to hospitalisation in the management of neuritis due to reactions in leprosy patients. The total mean cost per patient was approximately 7,234 rupees for ambulatory care versus 25,740 rupees for in-patient care. On average, patients receiving ambulatory care returned to work after 19.5 days, while hospitalized patients needed 66.8 days to return to work. Additionally, the study measured quality of life, but results for only 17 out of 26 patients were available. QOL scores improved in both groups, but the study did not find a significant mean difference in the pre- and post-treatment QOL scores between the two groups.

Remme 2006 estimated the average cost of POD for each new case of leprosy detected with disability at $44.10. The cost per DALY was calculated assuming a 25% self-cure rate, an average age of onset of 27, a disability weighting of 0.152, a life expectancy at age 25-29 of 44.75 (India data), and a 90% success rate. The cost per DALY for patients needing treatment for reactions and ulcers was estimated at $7, for those needing footwear and self-care education at $75, for those needing reconstructive surgery at $110.

DISCUSSION

Summary of main findings

Evidence for cost-effectiveness of POD interventions for leprosy is scarce. We found three studies; two were small, single-centre randomised controlled trials and one was a model-based review study. One trial found that canvas shoes were more cost-effective than plastazote shoes in healing and preventing ulcers and the other trial showed that ambulatory care was more cost-effective (lower cost and earlier return to work) compared to hospitalisation in the management of neuritis. The model-based study estimated the cost of POD interventions per DALY averted between

$7 and $110. None of the studies met all the quality criteria for economic evaluations. The cost perspective of the analysis, relevant and accurate costs, analysis of uncertainty in estimates, and issues of availability, affordability and sustainability were inadequately reported or addressed in the studies.

Generalisability

Generalisability of the findings is limited. The two trials [22,23] were conducted in a single centre and used prevailing or local prices to calculate costs. The economic evaluation was carried out alongside a randomised controlled trial and it has been argued that economic outcomes from such trials may differ significantly from usual practice or care [17]. The model-based study [24] stated that costs were likely to differ country by country and that the cost estimates should only be considered indicative, as they were based on limited published data and expert opinion. The cost of prevention of disability per new leprosy case with disability was expected to be higher than the estimate due to a backlog of old leprosy cases with disability, and this cost will be influenced by the numbers of multibacillary leprosy patients and the levels of disability in different settings and countries. The cost-effectiveness outcomes were also likely to vary, because these were based on limited effectiveness data, and the application of a disability weight of 0.152 to all patients may overestimate the benefits of interventions.

Issues of concern

One of the criteria for critically assessing economic evaluations was whether studies discussed all issues of concern. We focussed on issues of availability, affordability and sustainability, since these are current challenges in resource-poor countries and for neglected tropical diseases. Few studies have addressed one of these issues. Whilst self-care appears to be an effective, affordable and sustainable intervention to prevent disability in leprosy or lymphatic filariasis, when initially taught and supervised by general health staff [29-31], we are not aware of evidence that has documented the cost-effectiveness of self-care strategies. The ILA technical forum report highlighted the need for sustainable leprosy services through integrated general health services and provided basic requirements for this process, such as involvement, commitment and collaboration of the different stakeholders and health staff, strengthening of health systems, and careful planning [7]. Also, patients should be adequately informed about the availability of existing POD services [32].
Achieving universal coverage would require cost-effective POD interventions that can be delivered at adequate quality levels to all who need them and for as long as needed. Strategies for going to scale need to consider the context or setting of implementation (e.g. skilled staff and resources available, burden of disease, benefits to others than target group), the balance between quality and coverage levels, the choice of the health delivery system (e.g. general health services, disease-specific programmes, community-based health workers, or mix of alternatives), costs involved (e.g. strengthening health systems), and longer-term planning [9].

Strengths of the study

This is the first study that critically and systematically reviewed the existing literature on cost-effectiveness of interventions to prevent disability in leprosy. The search process was elaborate and to our knowledge no other studies were available for the review. We used a standard checklist to appraise the quality of economic evaluations of health care programmes and health interventions.

Limitations of the study

It is possible that not all of the relevant studies have been included in this review, and that we failed to find some unpublished ones. We contacted several experts in leprosy, but this did not reveal any unpublished or ongoing studies. We were not able to compare the cost-effectiveness of similar interventions or calculate standardised outcome estimates, due to lack of data on costs and effectiveness outcomes. Recently, two questionnaires on aspects of quality of life were developed and validated for chronically disabling conditions, such as leprosy, polio, spinal cord injuries and diabetes. One questionnaire (SALSA) measures limitations in daily activities [33], and the other one (Participation Scale) assesses perceived restrictions in social participation [34]. These questionnaires may be useful in assessing and comparing the effects of interventions and programmes for chronic and disabling conditions on patient-perceived changes in quality of life.

In conclusion, cost-effectiveness analysis should play an important role in the informed debate about issues of availability, affordability and sustainability of health care programmes or health interventions for chronically disabling diseases, such as leprosy, lymphatic filariasis, Buruli ulcer and diabetes, in resource-poor countries. It is recommended that future economic evaluation studies better define the cost perspective, the relevant alternatives, costs and outcomes of POD interventions, including adverse effects, and potentially uncertain variables, and to address issues of availability, affordability and sustainability. Future studies are needed to establish the cost-effectiveness of POD interventions and these should adhere to standard guidelines for economic evaluations.

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CHAPTER 10

General discussion

Research examining interventions to prevent disability in leprosy has produced a considerable body of evidence. This has led to more insights and better practice, but also to uncertainty about the best available evidence for treatment, tests and recommendations. Also, little is known about quality of life and cost-effectiveness of interventions to prevent disability in leprosy, while these are highly relevant for people affected by leprosy and policy makers. The main objective of this thesis was to evaluate the effectiveness of interventions to prevent disability in leprosy. In this chapter the research questions as posed in the introduction (p.10) will be answered (section 10.1), and conclusions and recommendations based on the findings of this thesis will be formulated (section 10.2).

10.1 ANSWERING THE RESEARCH QUESTIONS

Question 1

How effective are interventions for the prevention of permanent disability in people affected by leprosy?

Answer

Early detection is generally considered to be effective. There is no firm evidence of benefit for corticosteroids, decompressive surgery or interventions for ENL.

Comment

Detection delay, defined as the time between the patient noticing the first symptoms and health staff diagnosing leprosy, is a risk factor for impairment; longer delays increase the risk of presenting with impairment [1-4]. We examined the relationship between delay and impairment in two different patient populations from Bangladesh and Ethiopia and found that the relationship between delay and impairment was not the same across patient populations; with similar reported delays impairment rates were much higher in Ethiopia compared to Bangladesh, especially in PB leprosy patients. We concluded that leprosy control programmes should aim at both achieving short delays and addressing causes of delay specific to a population. Increased delay may be due to inadequate knowledge and awareness of leprosy and its early symptoms, more trust in traditional medicine as first action, misdiagnoses and stigma among health care staff, poor accessibility to health services and differences in leprosy control programmes [5-8].

Corticosteroids (prednisolone) are the cornerstone of management in acute nerve damage in leprosy, but our systematic review did not find long-term effects of corticosteroids (chapter 5). Steroids have some shortcomings. First, the nerve function recovery rate after treatment with steroids is highly variable (33-73%) [9]. This means that a substantial proportion of individuals, especially those with older nerve damage and chronic or recurrent reactions, does not respond

successfully to steroids [10]. Second, the optimal dose and duration of steroid treatment has not been established. The World Health Organization (WHO) recommends a standard 12-week course of prednisolone for severe reactions, starting at 40 mg daily and the dose being reduced every two weeks, with a maximum dosage of 1 mg prednisolone per kg of body weight [11], but several studies indicate that prolonged steroid courses are more beneficial since reactions often persist over many months [12-14]. Finally, steroid treatment may cause serious adverse events such as cataract, diabetes, hypertension, psychosis and peptic ulcer, but the risk of these events were not seen to be higher in individuals receiving standard steroid treatment compared to patients receiving placebo treatment [15,16]. Careful monitoring and awareness of adverse effects remains important for both standard and prolonged steroid regimens. New drugs, such as azathioprine and ciclosporin have been tested in small trials and may be steroid-sparing alternatives [17,18].

An alternative and frequently used treatment for nerve damage in leprosy is decompressive surgery. Our systematic review did not find an added benefit of surgery over prednisolone treatment (chapter 6). While only a few trials were identified, many non-randomised studies have been carried out. Relief of nerve pain and tenderness is the most frequently and consistently reported benefit. Nerve function improvement is frequently reported, but the response to surgery seems to depend on several factors, such as severity and duration of neuritis before surgery, the type of leprosy, the nerve involved and the surgical technique used [19-23].

Chapter 7 systematically assessed the effects of interventions for erythema nodosum leprosum (ENL). We found some benefit for thalidomide and clofazimine treatment, but generally we did not find clear benefits for interventions in the management of ENL. ENL is a complication known for its unpredictable nature, varying in severity and duration, and although treatments may be effective in controlling the acute symptoms of ENL, prevention of recurrences is far more difficult. New therapies, such as TNF-α antibody treatment, intravenous immunoglobulin, and tenidap, seem promising but need further investigation [24,25].

Question 2

How effective are interventions in preventing deterioration of disability in leprosy?

Answer

Evidence for the effectiveness of interventions aimed at preventing deterioration of disability is weak and little is known about their cost-effectiveness and quality of life impact.

Comment

A systematic review on interventions for skin changes caused by nerve damage found only weak evidence for the effectiveness of dressings with topical ketanserin or topical phenytoin in ulcer

healing and no statistically significant effect for any of the footwear tested. No RCTs assessing the effectiveness of self-care or educational interventions were identified [26].
Our systematic review that assessed the cost-effectiveness of interventions to prevent disability in leprosy showed that cost-effectiveness data are scarce and generally poorly reported (chapter 9). In 2006, a Consensus Development Conference on prevention of disability in chronically disabling conditions, such as leprosy, lymphatic filariasis, Buruli ulcer and diabetes was held and achieving universal coverage of self-care and footwear was identified as a priority issue [27]. Besides assessing the cost-effectiveness of these interventions, it is important to examine issues of implementation and feasibility in understanding the barriers and opportunities to achieving this with limited resources [28].

Quality of life outcome measures for leprosy disability have not yet been widely evaluated. Two assessment tools have been developed to measure either activity limitation (SALSA) [29] or social participation (Participation Scale) [30]. In one of our studies we used the SALSA and Participation Scale to prospectively assess trends in activity limitation and participation, and the effects of reconstructive surgery on these outcomes in individuals with hand or foot disability (chapter 8). We found a significant reduction in activity limitation one year after surgery. Participation was also improved, but not significantly. We interviewed 222 participants, 15 of whom took up the offer of surgery and 207 who did not. The main reasons for not having surgery were: no approval of family or husband, fear of surgery, being adjusted to the disability and experiencing a financial barrier. It is recommended to identify the need for surgery in a specific area or setting and to address barriers that prevent people from having surgery. The effects of surgery on functioning need to be further investigated in larger studies.

Question 3

How can programmes aimed at prevention of disability in leprosy be improved?

Answer

Programmes can be improved by establishing a package of interventions based on the best available evidence. The included interventions should be tailored to local needs now and in the future.

Comment

Systematic reviews showed that trials examining interventions to prevent disability in leprosy had generally small sample sizes, different outcomes and interventions and poor methodological quality [26,31-33]. It was highly recommended that future studies follow the current standards for design and reporting of RCTs, such as the CONSORT statement [34,35]. The importance of good clinical evidence has been advocated through 'evidence based medicine' and its key message is that the best available evidence from clinical research should guide clinical practice in making de-

cisions about the care of individuals [36]. This evidence does not always have to come from RCTs or systematic reviews; questions concerning the accuracy of diagnostic tests, the power of prognostic factors, or costs and quality of life impact of interventions cannot or need not to be answered by RCTs. Sometimes it is unclear whether guidelines and recommendations for practice have been supported by evidence from well-conducted research, while this is essential for maintaining effective leprosy control [37].

It is important to assess the need for proper treatment and follow-up, training in self-care and other prevention of disability interventions. In one of our studies (chapter 2) we predicted that there would still be a substantial number of people living with leprosy disability in the near future (about 0.8 to 1.1 million in 2020). This prediction was based on three different scenarios of annual declines in leprosy incidence (6%, 12%, 18% respectively) and the best available WHO data. Trends in prevalence and case detection will vary from country to country and studying changes over time is recommended to decide on interventions that meet the needs of a country or region.

Issues of availability, affordability and sustainability of leprosy services need to be addressed. Leprosy services in the longer term will have to be integrated into general health services and through community-based rehabilitation [38-40]. Successful integration in the community is not easy. First, general health services must be sufficiently available to meet the needs in a specific area and be accessible to people affected by leprosy. This asks for commitment and collaboration of all key stakeholders, such as the government and health care staff [38,41,42]. Second, general health care workers (GHWs) need training to understand the basics of leprosy diagnosis and treatment to address the specific needs of people affected by leprosy and to prevent disability [39,43]. Due to their many responsibilities and limited time, leprosy training for GHWs needs to be simple, easy to remember and effective. We evaluated three simplified tests to assess for nerve function impairment performed by newly trained GHWs as compared to a standard test conducted by experienced physiotherapists (chapter 4). We concluded that a simplified version of the standard test, as described in the ILEP Learning Guide Two [44], is a more useful tool for GHWs than a test derived from an Indian dance and a self-reporting questionnaire. It must be kept in mind that the main objective of the simplified tests is to screen for nerve function impairment in newly diagnosed patients and to refer for further assessment or treatment if necessary. A third issue is the need for effective referral systems to ensure that people diagnosed with nerve damage or reactions are easily sent to experienced staff or specialist centres, and for surveillance to monitor the number of newly detected cases or the number of cases with disability [39]. Finally, community-based interventions that are tailored to local and individual needs and preferences are of utmost importance. Effective community-based health education is needed to promote early self-reporting and reduce stigma in the community by teaching people about the early symptoms of leprosy, the availability of effective antibiotic treatment, and to involve them in the possibilities for prevention of disability and socio-economic rehabilitation [40,41].

10.2 CONCLUSIONS AND RECOMMENDATIONS

Conclusions

- It is important to identify and address causes of detection delay specific to a population.
- A simplified version of a standard test to assess for nerve function impairment is a useful diagnostic tool for primary health care workers.
- There is no firm evidence of benefit for corticosteroid treatment, decompressive surgery or interventions for type 2 leprosy reactions.
- Cost-effectiveness studies and quality of life data of interventions to prevent disability in leprosy are scarce.

Recommendations for research

It is recommended to investigate

- optimal steroid regimens for treating nerve damage and type 1 reactions;
- which patients or nerves will benefit most from decompressive surgery for treating nerve damage;
- optimal treatment of type 2 leprosy reactions, including prevention of recurrences;
- the role of other therapies for nerve damage and reactions, either alone or in combination with existing treatments;
- whether interventions improve quality of life and are cost-effective.

Recommendations for practice

- Policy makers should base guidelines and recommendations on the best available evidence.
- Clinicians should find effective ways for integrating research evidence and patient's values into clinical practice.
- Policy makers should develop strategies aimed at availability, affordability and sustainability of prevention of disability programmes.

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Summary

This thesis addresses the effectiveness of interventions to prevent disability in people affected by leprosy and the improvement of programmes aimed at prevention of disability.

Chapter 1 is an introduction to leprosy in general and disability and evaluation of interventions in particular. Although the global prevalence of registered leprosy patients receiving antibiotic (MDT) treatment has fallen below 1 per 10.000, still about 250,000 new leprosy cases were detected in 2007 and an estimated 2-3 million people who completed MDT treatment live with permanent physical disability due to the disease. Leprosy causes not only physical impairments, but also activity limitations and restrictions in social participation. People affected by leprosy often experience severe social, economic and psychological problems, such as difficulties in activities of daily living, unemployment, rejection of family and community, and mental distress. Prevention of permanent disability and deterioration of disability is therefore an important overall aim of leprosy control programmes and includes early detection and assessment of nerve damage, treatment of nerve damage and leprosy reactions, reconstructive surgery and socio-economic rehabilitation. Over the years much clinical and epidemiological research has been conducted in the field of prevention of disability in leprosy. This has led to more insights and better practice, but also to uncertainty about the best available evidence for clinical practice. The overall aim of this thesis was to evaluate the effects of interventions to prevent disability in people affected by leprosy and address implications for future leprosy control programmes. The three research questions were:

1. How effective are interventions for the prevention of permanent disability in people affected by leprosy?
2. How effective are interventions in preventing deterioration of disability in leprosy?
3. How can programmes aimed at prevention of disability in leprosy be improved?

Chapter 2 describes three scenarios of future trends in the global prevalence of people living with disability due to leprosy. In all three scenarios the number of newly detected people with leprosy decreases much more rapidly than the number of people living with disability. In the near future, we can still expect about one million people suffering from disability due to leprosy who need proper treatment and follow-up, and training in self-care and other prevention of disability interventions.

Chapter 3 describes the relationship between detection delay and leprosy disability at the time of detection in two different patient populations. Longer delays increased the risk of impairment, but the impairment rates by duration of delay varied considerably between the two populations, especially among PB leprosy patients. We concluded that early detection is effective in preventing disability, but that differences in delay and impairment across populations need to be identified and addressed.

Chapter 4 describes the use of three simplified tests to assess for nerve function impairment by general health workers. We considered a simplified version of a standard assessment as the most useful simplified test for general health workers with limited time and many responsibilities.
Chapter 5 presents results from a systematic review assessing the effects of corticosteroids for treating nerve damage and type 1 reactions. Two randomised controlled trials (RCTs) did not show a significant long-term effect. A third trial showed significant benefit of a prolonged steroid course. Further RCTs are needed to establish the long-term effectiveness and optimal regimens of steroids and to examine new therapies.
Chapter 6 presents results from a systematic review assessing the effects of decompressive surgery for treating nerve damage. Two trials did not show a significant added effect of surgery over steroid treatment alone. Well-designed RCTs are needed to establish the effectiveness of the combination of surgery and medical treatment compared to medical treatment alone.
Chapter 7 presents results from a systematic review assessing interventions for erythema nodosum leprosum (ENL) or type 2 reactions. We found generally insufficient evidence of benefit for interventions used in the management of ENL. Larger studies using clear definitions and assessing the effectiveness and optimal regimens of standard and new treatments are urgently required.
Chapter 8 describes the effects of reconstructive surgery on activity limitation and social participation in people with hand or foot disability. Participants who had surgery reported a statistically significant reduction in activity limitation and improved participation, but the number was small. Further needs assessment of surgery and evaluation of surgery in terms of activity limitation and participation in larger studies is recommended.
Chapter 9 presents results from a systematic review assessing the cost-effectiveness of interventions to prevent disability. We found that cost-effectiveness data are scarce and recommended to investigate which interventions offer value for money where resources are limited and to develop strategies aimed at available, affordable and sustainable services for leprosy.
Chapter 10 is a general discussion of the findings and provides answers to the research questions.

Conclusions

- It is important to identify and address causes of detection delay specific to a population.
- A simplified version of a standard test to assess for nerve function impairment is a useful diagnostic tool for primary health care workers.
- There is no firm evidence of benefit for corticosteroid treatment, decompressive surgery or interventions for type 2 leprosy reactions.
- Cost-effectiveness studies and quality of life data of interventions to prevent disability in leprosy are scarce.

Recommendations for research

It is recommended to investigate

- optimal steroid regimens for treating nerve damage and type 1 reactions;
- which patients or nerves will benefit most from decompressive surgery for treating nerve damage;
- optimal treatment of type 2 reactions, including prevention of recurrences;
- the role of other therapies for nerve damage and reactions, either alone or in combination with existing treatments;
- whether interventions improve quality of life and are cost-effective.

Recommendations for practice

- Policy makers should base guidelines and recommendations on the best available evidence.
- Clinicians should find effective ways for integrating research evidence and patient's values into clinical practice.
- Policy makers should develop strategies aimed at availability, affordability and sustainability of prevention of disability programmes.

Samenvatting

Dit proefschrift gaat in op de effectiviteit van interventies ter voorkoming van handicaps bij mensen met lepra en op het verbeteren van programma's die zich richten op het voorkomen van handicaps ten gevolge van lepra.

Hoofdstuk 1 geeft een algemeen overzicht van de ziekte lepra. Er wordt nader ingegaan op het begrip handicap ('disability') en op de evaluatie van interventies. Lepra is een infectieziekte en wordt veroorzaakt door een bacterie. Hoewel de ziekte besmettelijk is, worden de meeste mensen er niet ziek van. De leprabacterie heeft een voorkeur voor de koelere delen van het lichaam en tast vooral de huid en de zenuwen die net onder de huid liggen aan, waardoor verlammingen optreden en verlies van gevoel in met name ogen, handen en voeten. Hierdoor kunnen wonden en infecties ontstaan en uiteindelijk onherstelbare beschadigingen, zoals blindheid, klauwhanden en stompvoeten. Hoewel de prevalentie van het aantal geregistreerde leprapatiënten wereldwijd gedaald is tot minder dan 1 geval per 10.000 inwoners, werden er in 2007 nog altijd 250.000 nieuwe lepragevallen geregistreerd en hebben ongeveer 2-3 miljoen mensen permanente handicaps ten gevolge van lepra. Lepra veroorzaakt niet alleen fysieke beperkingen, maar ook belemmeringen in dagelijkse activiteiten en sociale participatie. Mensen met lepra ervaren vaak ernstige sociale, economische en psychische problemen, zoals werkloosheid, verstoten worden door familie en leefgemeenschap en depressiviteit. Een belangrijk doel van leprabestrijdingprogramma's is dan ook het voorkomen van permanente handicaps of het verergeren van bestaande handicaps. Preventie gebeurt door vroegtijdige opsporing en diagnose van zenuwbeschadiging, behandeling van zenuwbeschadiging en immunologische reacties, plastische chirurgie en sociaaleconomische rehabilitatie. In de afgelopen decennia is veel klinisch en epidemiologisch onderzoek gedaan naar preventie van de gevolgen van lepra. Dit heeft geleid tot meer inzicht en verbeterd klinisch handelen, maar ook tot meer onzekerheid over wat de beste wetenschappelijke onderbouwing is voor de praktijk. De algemene doelstelling van dit proefschrift was de effecten van interventies ter voorkoming van handicaps bij mensen met lepra te evalueren en in te gaan op de implicaties daarvan voor toekomstige leprabestrijdingprogramma's. De drie onderzoeksvragen waren:

1. Hoe effectief zijn interventies ter voorkoming van permanente handicaps bij mensen met lepra?
2. Hoe effectief zijn interventies ter voorkoming van verergering van bestaande handicaps bij mensen met lepra?
3. Hoe kunnen leprabestrijdingsprogramma's, die zich richten op preventie van handicaps, worden verbeterd?

Hoofdstuk 2 beschrijft drie scenario's met betrekking tot de wereldwijde prevalentie van mensen

met een handicap ten gevolge van lepra. In alle drie de scenario's nam het aantal nieuw ontdekte lepragevallen veel sneller af dan het aantal mensen dat leeft met een blijvende handicap. De verwachting is dat er in de nabije toekomst ongeveer één miljoen mensen zullen zijn die leven met de gevolgen van lepra en die zowel adequate behandeling als controle als begeleiding bij zelfzorg en andere vormen van preventie nodig hebben.

Hoofdstuk 3 beschrijft de relatie tussen vertraagde opsporing en de aanwezigheid van handicaps op het moment van opsporing in twee verschillende patiëntengroepen. Voor beide patiëntengroepen gold dat hoe langer het duurde voordat iemand ontdekt was met lepra, des te groter de de kans was dat die patiënt al een handicap had. De twee patiëntengroepen verschilden echter ten aanzien van het percentage invalide personen als gekeken werd naar hoe lang het duurde voordat iemand ontdekt was. Dit was met name het geval bij paucibacillaire leprapatiënten. De conclusie was dat, hoewel effectieve preventie begint met vroegtijdige opsporing, het goed is te onderzoeken waarom bij de ene patiëntengroep meer mensen met handicaps worden ontdekt bij eenzelfde opsporingsduur dan bij de andere groep van patiënten.

Hoofdstuk 4 beschrijft het gebruik van drie vereenvoudigde testen door medewerkers in de primaire gezondheidszorg om zenuwbeschadiging bij leprapatiënten te diagnosticeren. Voor gezondheidsmedewerkers die veel verschillende verantwoordelijkheden hebben en beperkte tijd, werd een vereenvoudigde versie van de standaard test als meest betrouwbaar en bruikbaar gezien voor het opsporen van zenuwbeschadiging bij leprapatiënten.

Hoofdstuk 5 geeft de resultaten weer van een systematisch onderzoek naar de effecten van corticosteroïden voor de behandeling van zenuwbeschadiging en type 1 leprareacties. Er werd geen significant langetermijneffect gevonden in twee gerandomiseerde, gecontroleerde onderzoeken en geen significant voordeel van een verlengde steroïdenkuur in een derde gerandomiseerd, gecontroleerd onderzoek. Er zijn meer gerandomiseerde, gecontroleerde onderzoeken nodig om de effectiviteit op lange termijn en de optimale dosis en duur van behandeling met steroïden vast te stellen. Er is tevens onderzoek nodig naar nieuwe behandelingsmogelijkheden voor zenuwbeschadiging ten gevolge van lepra.

Hoofdstuk 6 geeft de resultaten weer van een systematisch onderzoek naar de effecten van decompressiechirurgie voor de behandeling van zenuwbeschadiging. Er werd geen significant toegevoegde waarde gevonden voor chirurgie vergeleken met behandeling met alleen steroïden in twee gerandomiseerde, gecontroleerde onderzoeken. Er zijn gerandomiseerde, gecontroleerde onderzoeken van goede methodologische kwaliteit nodig om de effectiviteit van chirurgie in combinatie met medicinale behandeling ten opzichte van behandeling met alleen steroïden vast te stellen.

Hoofdstuk 7 geeft de resultaten weer van een systematisch onderzoek naar de effecten van interventies voor de behandeling van erythema nodosum leprosum (ENL) of type 2 leprareacties. Over het algemeen werd er onvoldoende wetenschappelijke onderbouwing gevonden voor interventies voor ENL. Er zijn grotere en helder gedefinieerde studies nodig die de effectiviteit en optimale dosis en duur van behandeling van standaard- en nieuwe behandelingsmogelijkheden evalueren.

Hoofdstuk 8 beschrijft de effecten van plastische chirurgie op beperkingen bij dagelijkse activiteiten en sociale participatie van mensen met fysieke problemen ten gevolge van lepra. Deelnemende personen die chirurgisch behandeld waren, rapporteerden een significante verbetering in dagelijkse activiteiten en niet-significant verbeterde sociale participatie, maar hun aantal was te klein om definitieve conclusies te trekken. Er is meer onderzoek nodig naar de behoefte aan chirurgie onder mensen met een behandelbare handicap en grootschaliger onderzoek naar de effecten van chirurgie op dagelijkse activiteiten en sociale participatie.
Hoofdstuk 9 geeft de resultaten weer van een systematisch onderzoek naar de kosteneffectiviteit van interventies ter voorkoming van handicaps. Er werden weinig data gevonden. Het is van belang te onderzoeken welke interventies kosteneffectief zijn en strategieën te ontwikkelen die gericht zijn op toegankelijke, betaalbare en duurzame leprazorg.
In **hoofdstuk 10** worden de bevindingen bediscussieerd en worden de onderzoeksvragen beantwoord.

Conclusies

- Het is belangrijk te onderzoeken wat populatiespecifieke oorzaken zijn van vertragingen in opsporing van leprapatiënten.
- Een vereenvoudigde versie van de standaardtest om zenuwbeschadiging op te sporen is een bruikbare diagnostische test voor medewerkers in de primaire gezondheidszorg.
- Er is geen stevige wetenschappelijke onderbouwing voor een significant gunstig effect van behandeling met corticosteroïden, decompressiechirurgie of behandeling voor type 2 leprareacties.
- Er is tot nu toe weinig onderzoek gedaan naar de kosteneffectiviteit en kwaliteit van leven van interventies ter voorkoming van handicaps door lepra.

Aanbevelingen voor onderzoek

Het is aan te bevelen onderzoek te doen naar:

- de optimale dosis en duur van behandeling met corticosteroïden voor de behandeling van zenuwbeschadiging en type 1 reacties;
- welke patiënten of type zenuwen het meeste voordeel hebben van decompressiechirurgie voor de behandeling van zenuwbeschadiging;
- de optimale behandeling voor type 2 reacties, inclusief preventie van recidiverende reacties;
- de rol van nieuwe behandelingsmogelijkheden voor zenuwbeschadiging en reacties, op zichzelf staand of in combinatie met bestaande behandelingen;
- de verbetering van de kwaliteit van leven en de kosteneffectiviteit van interventies.

Aanbevelingen voor de praktijk

– Beleidsmakers dienen richtlijnen en aanbevelingen te baseren op de best beschikbare wetenschappelijke onderbouwing.
– Professionals in de gezondheidszorg dienen effectieve manieren te vinden om zowel wetenschappelijke onderbouwing als patiëntenvoorkeuren te integreren in de dagelijkse praktijk.
– Beleidsmakers dienen strategieën te ontwikkelen die gericht zijn op toegankelijkheid, betaalbaarheid en duurzaamheid van programma's voor de preventie van handicaps ten gevolge van lepra.

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Natasja

Curriculum Vitae

(photo by Marion Dubbelman, www.mariondubbelman.nl)

Natasja van Veen (1978) was born in South Korea, but grew up in the Netherlands. After graduating from the Greijdanus College (gymnasium) in Zwolle in 1997, she began studies in Home Economics and Human Ecology at Wageningen University and passed the propedeutical exam (cum laude) in 1998. In 1999 she continued further studies in Health Sciences at Maastricht University and graduated in 2004. From 2001 to 2004 she worked as a student assistant at the Department of Human Movement Sciences. In 2003 she participated as a research assistant in a multidisciplinary fall prevention project at the Department of Health Care studies of Maastricht University. During her time as a student she was actively involved in the Christian students associations Ichthus Wageningen and Ichthus Maastricht. She was member (treasurer) of the organising committee of the annual national conference, the 'Retraite' in 1999. From 2001 to 2002 she was the chairperson of C.S.V. Ichthus Maastricht. In October 2004 she started as a PhD student at the Department of Public Health of Erasmus MC, University Medical Center Rotterdam. Her research project addressed the effectiveness of interventions to prevent disability in leprosy. In 2007 she obtained the Masters degree in Public Health. Since May 2009 she works as a consultant at the Orde van Medisch Specialisten (Dutch Association of Medical Specialists). She is married to Tjebbe van Oostenbruggen.

Publications

1. **van Veen NHJ**, Meima A, Richardus JH. The relationship between detection delay and impairment in leprosy control: a comparison of patient cohorts from Bangladesh and Ethiopia. *Leprosy Review* 2006; 77(4):356-65.
2. **van Veen NHJ**, Nicholls PG, Smith WCS, Richardus JH. Corticosteroids for treating nerve damage in leprosy. *Cochrane Database of Systematic Reviews* 2007; (2):CD005491.
3. Meima A, **van Veen NHJ**, Richardus JH. Future prevalence of WHO grade 2 impairment in relation to incidence trends in leprosy: an exploration. *Tropical Medicine & International Health* 2008; 13(2):241-6.
4. **van Veen NHJ**, Schreuders TAR, Theuvenet WJ, Agrawal A, Richardus JH. Decompressive surgery for treating nerve damage in leprosy. *Cochrane Database of Systematic Reviews* 2009; (1):CD006983.
5. **van Veen NHJ**, McNamee P, Richardus JH, Smith WCS. Cost-effectiveness of interventions to prevent disability in leprosy: a systematic review. *PLoS One* 2009; 4(2): e4548.
6. **van Veen NHJ**, Richardus JH. Evidence based practice in leprosy: where do we stand? *Leprosy Review* 2008; 79(4):353-7.
7. **van Veen NHJ**, Nicholls PG, Smith WCS, Richardus JH. Corticosteroids for treating nerve damage in leprosy. A Cochrane review. *Leprosy Review* 2008; 79(4):361-71.
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9. **van Veen NHJ**, Anne E. Roberts AE, Mahato ME, Velema JP. Evaluation of simplified tests for the diagnosis of nerve function impairment in leprosy: the Sensory Motor Screening (SMS) study. *Leprosy Review* 2009; 80(1):51-64.
10. **van Veen NHJ**, Lockwood DNJ, van Brakel WH, Ramirez J Jr, Richardus JH. Interventions for erythema nodosum leprosum. *Cochrane Database of Systematic Reviews* 2009; (3): CD006949.
11. **van Veen NHJ**, Lockwood DNJ, van Brakel WH, Ramirez J Jr, Richardus JH. Interventions for erythema nodosum leprosum. A Cochrane Review. (*submitted to Leprosy Review)*
12. **van Veen NHJ**, Hemo DA, Bowers LR, Pahan D, Negrini JF, Velema JP, Richardus JH. Evaluation of activity limitation and social participation, and the effects of reconstructive surgery in people with disability due to leprosy: a prospective cohort study. *(submitted to Lancet)*

Erasmus MC
Universitair Medisch Centrum Rotterdam

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: Natasja H.J. van Veen Erasmus MC Department: Public Health	PhD period: 2004-2009 Promotor: Prof. dr. J.D.F. Habbema Supervisor: Dr. J.H. Richardus

	Year	Workload (Hours/ECTS)
1. PhD training		
Research skills		
- Master of Public Health, Netherlands Institute for Health Sciences (Nihes), Rotterdam, Netherlands	2004-07	30 ECTS
In-depth courses (e.g. Research school, Medical Training)		
- Summer course Health Economics, Netherlands Institute for Health Sciences (Nihes), Rotterdam, Netherlands	2008	0.7 ECTS
International conferences and presentations		
- Consensus Development Conference on the Prevention of Disability, Cebu City, Philippines	2006	32 hours
- 5th European Congress on Tropical Medicine and International Health, Amsterdam, Netherlands:	2007	24 hours
▪ Delay as indicator in leprosy control		
- 17th International Leprosy Congress, Hyderabad, India:	2008	72 hours
▪ Evidence base of interventions to treat nerve damage in leprosy		
▪ Evaluation of simplified tests for the diagnosis of nerve function impairment in leprosy: Sensory Motor Screening (SMS) study		
▪ Prospective Assessment of Surgery and Quality of Life Study		
Seminars and workshops		
- NWO Talent Day, Utrecht, Netherlands	2006	8 hours
- International Workshop on Neuropathology in Leprosy, Soesterberg, Netherlands	2007	32 hours
- DCDD International Conference: Sport and Disability in Development Cooperation, Utrecht, Netherlands	2007	8 hours
- Workshop Presenting Science, Erasmus University Rotterdam, Netherlands	2008	12 hours
- Workshop Identifying and expanding your network, Erasmus University Rotterdam, Netherlands	2008	8 hours
Other		
- Progress report annual meeting, Netherlands Leprosy Relief, Amsterdam, Netherlands	2005-08	32 hours
- Co-ordinator discussion meetings, section Infectious Diseases, Department of Public Health, Erasmus MC Rotterdam, Netherlands	2005-08	10 hours
- Member of seminar committee, Department of Public Health, Erasmus MC Rotterdam, Netherlands	2007-09	20 hours
- Study visit to section of Population Health (Prof. W.C.S. Smith) and Health Economics Research unit (Dr. P. McNamee), University of Aberdeen, Scotland	2008	240 hours
2. Teaching activities		
Other		
- Revising essays of STOLA tropical course, STOLA Foundation, Rotterdam, Netherlands	2006-08	15 hours