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Review of Leprosy Research Evidence (2002 – 2009) and Implications for Current Policy and Practice

ILEP Technical Commission

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Summary

Introduction

The ILEP Technical Commission (ITC) advises ILEP member associations on technical aspects of leprosy. A major review of research evidence in leprosy was published prior to the International Leprosy Congress in 2002. This current report updates that review based on research published between 2002–2009 and focuses on interventions for prevention, early diagnosis, chemotherapy, reactions, prevention of disability, stigma measurement and reduction and rehabilitation in leprosy.

Methods

A systematic search of electronic databases of published literature for systematic reviews, controlled trials and ongoing trials was conducted in July 2009. The search identified 13 reviews and 21 controlled trials. The data from these studies were extracted and the references cited by these studies reviewed. Each member of the ITC took responsibility to review this evidence for each of the 7 topics and prepared a report summarising the evidence and making recommendations. These findings were presented and discussed at a Forum held in London in March 2010. The report was finalised following this Forum. The evidence was graded using a standard grading system for levels of evidence. However for some topics the evidence used qualitative and other designs which do no conform to this grading but was considered relevant and appropriate.

This review uses both paradigms of evidence to generate recommendations which are categorised as:

- Evidence Based (EB) where supported by strong evidence,
- Best Practice (BP) when evidence is weak or lacking, and
- (R) for areas considered as a priority for research.

Summary and Recommendations

1. PREVENTION

a. Immunoprophylaxis

BCG is the most widely used vaccine and it has been known for a long time that it offers some protection against leprosy, although the effect varies greatly from country to country. Although there are new reviews, the evidence concerning BCG has not changed significantly. A second dose of BCG given to the general population was found to have little value in adding further protection against leprosy. One study of immunization of household contacts with *Mw* in India showed reasonable protection declining over a 9-year period. A poorly designed cohort study on the use of BCG in contacts of leprosy cases in Brazil suggests some

benefit, although the results must be viewed with caution. Both studies of immunization of leprosy contacts found a significant increase in cases reported in the first year in the immunized groups.

Leprosy control programs should support the continued use of BCG for all infants in endemic areas (EB).

Since chemoprophylaxis in contacts with single-dose rifampicin provides protection only in the first two years and immunization of contacts appears to provide protection only after the first year, it would seem reasonable to study the effectiveness of a combined strategy (R).

b. Chemoprophylaxis

A new, large randomised controlled trial of giving a single dose of rifampicin to close contacts of newly diagnosed leprosy patients was about 57% efficacious in reducing new cases of leprosy but only for the first 2 years of follow-up.

The Enhanced Global Strategy for Leprosy has recommended the exploration of the use of chemoprophylaxis as a tool to prevent the occurrence of new leprosy cases among household contacts as a result of this finding.

Pilot projects on implementing chemoprophylaxis under routine programme conditions are recommended to assess acceptability, cost-effectiveness, feasibility, and ethic issues (EB).

Further study of blanket chemoprophylaxis is merited, particularly in light of the increasing use of blanket approaches in tackling other Neglected Tropical Diseases (R).

Further research is recommended in improving the effectiveness of chemoprophylaxis through development of the regimen (R).

2. EARLY DIAGNOSIS

There are two new reviews of studies of early case-detection. One review shows that there is an increased risk of leprosy in contacts, but the definition of a contact needs to include both people in the same household and others, such as neighbours and social contacts. The other review shows that individual counselling of new cases can help in identifying other new cases, but there are so few good evaluations of general health education efforts that no statement about its effectiveness in promoting early case detection can be made with confidence.

Further evaluation of health education activities, including those that are targeted at certain groups such as teachers or women (BP)

Operational research on ways of identifying appropriate groups of contacts and then arranging for counselling, examination and treatment (when necessary), possibly in conjunction with chemoprophylaxis (R).

Further work on the development and assessment of immunological and molecular markers for infection with M leprae and early disease (R).

3. CHEMOTHERAPY

Very little solid evidence has emerged since the ILA Technical Forum of 2002 permitting any recommendations for drastic changes in the WHO MDT regimens. U-MDT trials are under way, but several years of follow up will still be necessary before being able to draw firm

conclusions. The bactericidal activity of fluoroquinolones against *M. leprae* has been further studied and confirms their possible role as part of future and more potent multidrug therapy regimens. There is still a need to continue research for new, shorter, possibly fully supervised, MDT regimens, based on the combination of highly bactericidal drugs.

Follow-up of present studies of U-MDT must be ensured, in order to be able to draw firm conclusions on the possibility to reduce the duration of WHO MDT to six months for MB leprosy patients (R).

Additional data must be collected on relapse rates after the 12-month MDT regimen for MB leprosy (R).

Trials of new, shorter, possibly fully supervised, MDT regimens, based on the combination of highly bactericidal drugs such as rifapentin, moxyfloxacin, clarithromycin, minocycline, or others, should be launched (R).

New drugs or new regimens should be developed for patients with rifampicin resistance or those presenting signs of intolerance (R).

4. REACTIONS

The optimum length of steroid treatment is not known, although some data shows that a longer course might be better but this was a study using non-standardised scales (20 weeks treatment is superior to 12 weeks in one study). The optimum dose of steroids is not known although so far no studies have shown an advantage for higher doses. No studies have been done using a dose per weight regimen in patients. There is a 20–50% relapse rate after patients have received steroid treatments and the aetiology and optimum management of this needs defining. Standardised tools are needed to measure outcomes in trials of patients with reactions so that studies are comparable. Second line drugs for the treatment of reactions for patients who do not respond to prednisolone are also needed. HIV and leprosy co-infection often present with a T1R and the optimum management of this needs defining.

Standardised tools are needed to measure outcomes so that studies are comparable (BP).

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

For Type 1 reactions and nerve damage

Large studies are urgently needed to determine the optimum dose and duration of prednisolone treatment of nerve damage and T1R (R).

Large studies are also needed in Africa and Brazil because most of the data comes from the Indian sub-continent. (India, Bangladesh and Nepal) (R).

Second-line treatments need to be evaluated for patients who do not respond to prednisolone (R).

For Erythema Nodosum Leprosum

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

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 (R).

The development of a safe and effective alternative to both steroids and thalidomide (R).

5. PREVENTION OF DISABILITY

In September 2006 available evidence and reports of best practice of POD were reviewed at the Consensus Development Conference (CDC) which was convened in Cebu, The Philippines. The aim of the CDC was to present a consensus document on POD. The document outlines best practice and provides guidance for the implementation of POD for national programmes that followed the recommendations in the WHO Revised Global Strategy. This review focuses primarily on research findings published since 2006.

Self Care – The most pressing need for information regarding self-care relates to operational factors. Health Systems Research in low income countries is required to establish what constitutes 'adequate resources' and how they can be used to optimal effect (BP).

Footwear – a randomised control trial comparing force attenuating properties of materials commonly used for commercial footwear production should be undertaken (R).

Wound Care – the optimal concentrations of topical sodium diphenylhydantoin (DpH) (phenytoin) as a treatment for wound care in an institutional environment need to be determined, and its cost effectiveness should be established (R).

Bone Density – Evidence is required to establish the ideal dosage and long term outcomes from the use of bisphosphonates as an adjunctive pharmacological therapy for neurological bone disorganisation, and the cost effectiveness and efficiency of Residronate should be established (R).

Neurolysis – random control trials are still required to establish the efficacy of neurolysis, the factors that might predict favourable responses, and the impact on quality of life (R).

6. STIGMA

No less than 56 papers were published between 2003 and 2009 addressing leprosy-related stigma. Of these, 37 were either reviews on stigma or reports from actual stigma-related studies. A much wider review was conducted to include contributions from disciplines working with other stigmatised conditions (e.g. HIV and mental health). We focussed mainly on measurement of stigma and interventions to reduce stigma in the more direct leprosy-related literature.

Future research on leprosy-related stigma should take multiple perspectives (cultural, religious, historic and structural/political) into account with regard to the process of stigmatisation (BP).

Emancipatory research should be encouraged in which affected persons take the lead in investigations and in which their specific and unique contributions are acknowledged (BP).

Lessons should be learnt from stigma research outside the field of leprosy, such as HIV/AIDS and mental health (BP).

Randomised controlled trials are needed of stigma reduction interventions and of various approaches to counselling (R).

Validation studies should be conducted to test the psychometric properties of stigma measurement instruments, also when instruments are introduced in new cultural or language settings (R).

Comparative studies should be conducted to determine the optimal instruments for measuring particular aspects of stigma (R).

7. REHABILITATION

The literature review provides more evidence for wider application of community-based and self care strategies. In terms of new areas that also require research, there are issues of human rights approaches, the new UN Convention on disability and involvement of organisations of affected persons in planning and implementation of rehabilitation strategies. Many of these issues have been already raised in recent publications like the WHO-ILEP joint publication (Technical Guide on CBR).

There is need to further promote and build on involvement of persons affected with leprosy in all aspects of their care and rehabilitation with emphasis on CBR and on holistic view of rehabilitation needs (EB).

Rehabilitation activities can be organised and monitored in terms of the CBR matrix, for ensuring that all the different needs of persons affected with leprosy are considered including self-care and socio-economic rehabilitation (BP).

Understanding the principles and practices of a 'human rights approach' in practical implementation of rehabilitation activities in the field conditions (BP).

Defining the components of a 'holistic' approach towards rehabilitation including self-care, footwear and mobility aids, SER, education, advocacy and lobbying for rights and services. Role of persons affected with leprosy and their organisations in all aspects of their care and rehabilitation requires a specific focus (R).

Review of Leprosy Research Evidence (2002–2009) and Implications for Current Policy and Practice

Introduction

Research and development is part of the ILEP Technical Commission's (ITC) Plan of Work for 2008–2011. The activity is defined as a synthesis of research findings for implementation and development of research strategy based on priority research questions including chemotherapy. This was agreed by the ILEP Board in 2008 following the ILEP Technical Forum.

The last major review of research evidence in leprosy was conducted prior to the 2002 International Leprosy Congress and was published in Leprosy Review[1] and in the International and Indian Journals of Leprosy. The review would focus on the following areas:

1. Prevention
2. Early diagnosis
3. Chemotherapy
4. Reaction
5. Prevention of disability
6. Stigma measurement and interventions
7. Rehabilitation

Methods

Literature searches using electronic bibliographic databases were conducted in 2009 based on the 7 selected topics listed above. The search focused on systematic reviews and controlled trials. A further search was made to identify ongoing trials. The methods of the identified studies were critically appraised using a standardised checklist and abstracts prepared. These abstracts along with the original papers were sent to the members of the ITC who reviewed these papers and added other research evidence considered relevant and published since 2002. Reviews of the research evidence were then prepared by the relevant members of the ITC.

1. SYSTEMATIC REVIEWS

A systematic search of electronic databases of the published literature for systematic reviews was conducted. The databases EBM REVIEWS, MEDLINE, EMBASE and CAB ABSTRACTS were searched with the criteria of 2002-current (June 2009), limited to humans, English and to systematic reviews. The search terms used were 'leprosy' OR 'Hansen's disease' OR 'mycobacterium leprae' AND one of the following search terms 'early diagnosis', 'diagnosis', 'multidrug therapy' OR 'MDT', 'drug resistance', 'new regimens', 'chemoprophylaxis', 'reaction detection', 'treatment', 'prevention of disability', 'stigma', 'intervention', 'rehabilitation'. The Cochrane Database of Systematic Reviews, Leprosy Review and the International Journal of Leprosy and other Mycobacterial Diseases were also searched for relevant articles. Publications by ILEP or WHO were also searched.

The references cited by the relevant articles were also reviewed. A total of 13 systematic reviews were identified and critically appraised. The data were extracted using the same format as was used for the Report of the ILA Technical Forum in 2002.[1]

2. CONTROLLED TRIALS

The same procedure was followed when searching the published literature for randomised controlled trials with the search being amended to include only randomised controlled trials. The *Cochrane Central Register of Controlled Trials* was also searched. The 21 identified controlled trials were critically appraised and data extracted using a similar format.

3. ONGOING TRIALS

In addition to this a search of ongoing clinical trials (www.controlled-trials.com) using the search term 'leprosy' revealed 27 results of which 8 were deemed relevant. Two more relevant ongoing studies were further identified.

4. CRITICAL APPRAISAL, LEVELS OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

An Annex of the completed data extract forms for each of the 13 reviews, for each of the 21 RCTs, and details of the ongoing studies are available on the ILEP website (http://www.ilep.org.uk/)

Biomedical research can be graded in terms of the level of evidence based on the study design and the quality of the research where a systematic review of randomised controlled trials forms the highest level. This system for grading evidence proposed by the centre for Evidence Based Medicine[2] has been used in this review of the literature.

Levels of Evidence (March 2009):

1a	Systematic review of randomised controlled trials
1b	Individual randomised controlled trial
1c	All or none
2a	Systematic review of cohort studies
2b	Individual cohort study
2c	Outcomes research/ecological study
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series
5	Expert opinion

However there are other forms of evidence which do not conform to these biomedical grades but which are valid and relevant. These include qualitative methods, social science approaches and policy analyses. These are particularly relevant to areas such as preventing disability, stigma reduction and community based rehabilitation. This review uses both paradigms of evidence to generate recommendations which are categorised as Evidence Based (EB) where supported by strong evidence, Best Practice (BP) when evidence is weak or lacking, and (R) for areas considered as a priority for research.

5. PRESENTATION OF FINDINGS: REVIEW OF RESEARCH EVIDENCE

The research reviews have been prepared led by the individual ITC member who reviewed the literature. These have been structured into 7 sections as follows: Prevention – Immunoprophylaxis (Saunderson) and chemoprophylaxis (Smith), Diagnosis (Saunderson), Chemotherapy (Declercq), Reactions (Lockwood), Prevention of disability (Cross), Stigma (van Brakel), and Rehabilitation (Deepak).

References

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1. Prevention – Immunoprophylaxis and Chemoprophylaxis

W. Cairns Smith & Paul Saunderson

a. Review of recent literature on Immunoprophylaxis

Summary

BCG is the most widely used vaccine and it has been known for a long time that it offers some protection against leprosy, although the effect varies greatly from country to country. Although there are new reviews, the evidence concerning BCG has not changed significantly and leprosy control programs should support the continued use of BCG for all infants in endemic areas. A second dose of BCG given to the general population has little value in adding further protection against leprosy.

One study of immunization of household contacts with *Mw* in India showed reasonable protection declining over a 9-year period. A poorly designed cohort study on the use of BCG in contacts of leprosy cases in Brazil suggests some benefit, although the results must be viewed with caution. Both studies of immunization of leprosy contacts found a significant increase in cases reported in the first year in the immunized groups.

Recent evidence

We identified 3 systematic reviews, 1 case-control study and 2 controlled trials meeting the criteria for analysis. A further cohort study is discussed.

In the first systematic review[1] the focus is on the prevention of tuberculosis (TB) using Bacille Calmette Guerin (BCG), but in several trials since 1960, carried out in six countries, the effect of BCG on leprosy was also measured. The first dose of BCG gave protection of between 14% and 80% against leprosy, while a second dose gave protection of between 0% and 50%. While a definite protective effect has been demonstrated, the effect is variable, making it impossible to generalize and calculate a summary estimate of protection.

Adverse reactions after BCG administration do occur: local reactions that are short-lived and benign are common. Ulceration at the vaccination site and suppurative lymphadenitis may occur at frequencies of between 0·1 and 5 cases per 1000 vaccinations. Disseminated BCG infection is rare, but can cause death; the incidence in older studies was between 0·19 and 1·56 cases per one million vaccinations. More recently, the incidence was estimated at 205 per one million vaccinations, related to congenital or acquired immunodeficiency. Current recommendations are that BCG can be given to HIV positive infants, but is contraindicated in those with clinical signs of immunodeficiency.

The second systematic review[2] looked specifically at the role of BCG in preventing leprosy. It included experimental studies (1 randomized and 6 non-randomized controlled trials) and observational studies (19 cohort and case control studies). Meta-analysis of the seven experimental studies found an overall protective effect of 26% (95% CI 14% to 37%) after 5–16 years of follow up. Meta-analysis of the 19 observational studies found an overall protective effect of 61% (95% CI 51% to 70%) at 4–5 years of follow up. The authors noted

that the observational studies tended to overestimate the protective effect of BCG, possibly because they had a shorter period of follow up compared with the experimental studies, and protective efficacy seems to decrease with time. The third systematic review[3] examined a similar pool of studies included in the second review already quoted, with similar results.

A more recent case-control study in Brazil looked at the incidence of leprosy in adults with and without a BCG scar, and without known contact with a case of leprosy.[4] Where BCG had been given, it was deemed most likely to have been given at birth. The results suggested good protection (85%; 95% CI 77–92%) against leprosy in those under 30 years of age, moderate protection (54%; 95% CI 37–85%) in those between 30 and 39 years of age, and no significant protection in those over 40 years.

Two randomized controlled trials examined the use of Immunoprophylaxis in specific contexts. Sharma[5] looked at the effect of *Mycobacterium w* given to household contacts (HHC) in Uttar Pradesh, India. 24 060 HHC were randomized to receive either two doses of *Mw*, or placebo (average of 4·8 HHC per index case). All new cases of leprosy found during the first year after vaccination were excluded from the analysis, as they were deemed to be incubating leprosy already at the time of immunization (the number of cases is not given). Follow-up examinations were then done after 3, 6 and 9 years. Protection of 69%, 59% and 39% was observed during the respective surveys.

In the second trial,[6] BCG revaccination was administered to randomly selected clusters of school children in Manaus, Brazil; 42 662 children aged between 7 and 14 years received the intervention. Control groups (57 108 children) received no intervention. The incidence rate ratio for leprosy after 6·7 years of follow-up, was 0·99 (95% CI 0·68–1·45), indicating no protective effect from a second dose of BCG.

A further cohort study should be mentioned. Düppre[7] examined the effectiveness of BCG vaccination given to contacts of leprosy cases seen at Fiocruz in Rio de Janeiro. 3536 contacts were identified between 1991 and 2005 and given BCG; a control group, consisted of contacts who were identified before the policy of vaccinating all contacts was introduced, plus further contacts identified after 1991, who for various reasons were not vaccinated. There were 58 cases of leprosy in the vaccinated group of 3536 individuals (21 cases occurring during the first year after vaccination), and 64 cases in the unvaccinated group of 1810 individuals (7 cases occurring in the first year after recruitment). The authors state that the protection conferred by BCG in contacts was 56% and that it was not substantially affected by previous BCG vaccination (50% protection in those with a scar and 59% in those without). The risk of tuberculoid leprosy during the initial months was high among those vaccinated with no scar; if the first year cases are excluded from the analysis, the protective effect is 80%. A major problem with this study is that the control group is not strictly comparable with the intervention group and the follow-up period for the two groups is substantially different.

Recommendations for further research

Immunization of contacts may be of benefit, although the precipitation of overt paucibacillary cases in the first year is a concern; two issues should be considered in the design of new studies:

- Recent findings from studies on risk factors in contacts suggest that a larger number of contacts should be recruited for each index case (for example, 20 contacts per case seems to be more appropriate than 5 contacts per case).
- Since chemoprophylaxis in contacts with single-dose rifampicin provides protection only in the first two years and immunization of contacts appears to provide protection only after the first year, it would seem reasonable to study the effectiveness of a combined strategy.

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b. Review of recent literature on Chemoprophylaxis

Summary

A new, large randomised controlled trial of giving a single dose of rifampicin to close contacts of newly diagnosed leprosy patients was about 57% efficacious in reducing new cases of leprosy but only for the first 2 years of follow-up. The Enhanced Global Strategy for Leprosy has recommended the exploration of the use of chemoprophylaxis as a tool to prevent the occurrence of new leprosy cases among household contacts as a result of this finding. Pilot projects on implementing chemoprophylaxis under routine programme conditions are recommended to assess acceptability, cost-effectiveness, feasibility, and ethic issues.

Recent Evidence

No new systematic reviews of chemoprophylaxis have been published in this period, the previous systematic review was largely based on dapsone or dapsone related prophylaxis.

A number of important trials were published in this period on the chemoprophylaxis in leprosy. The trial reported by Oo[1] used serological response as a proxy outcome measure and the trial by Saikawa[2] also used immunological tests as an outcome.

The study reported by Bakker[3] was based on a group of islands in Indonesia with a control group, a group where only contacts of leprosy cases received chemoprophylaxis and a group where the total island population received blanket chemoprophylaxis. The yearly incidence of leprosy was significantly lower after three years in the blanket group compared to the control group but there was no difference in the group where only contacts received prophylaxis. The finding of the effect in the blanket group is comparable to the observation of greater efficacy in the blanket use of dapsone prophylaxis compared to its use in contacts. This merits further study particular in light of the increasing use of blanket approaches in tackling other Neglected Tropical Diseases. Blanket approaches have been used in other settings such as Micronesia and the Maldives but not using designs from which conclusions could be drawn.

The major trial of chemoprophylaxis reported in this period is that published by Moet[4] based on a trial conducted in Bangladesh. The large trial randomised the contacts of 1037 newly diagnosed leprosy patients to receive a single dose of rifampicin or placebo. There was a significant 57% reduction in new cases in the first two years but not further reduction in the 3rd and 4th years of follow up. This provides grade 1 evidence for recommending rifampicin prophylaxis in contacts. This has been accepted by the global programme and pilot studies of the acceptability, cost-effectiveness, feasibility, and ethic issues are recommended. Subgroup analysis showed that the effect was not the same for any contacts, those not closely related or who lived further away benefited more – these findings have implications for the understanding the process of transmission and immune responses. BCG was shown to have a complementary effect to rifampicin in preventing leprosy.

The emerging evidence on chemoprophylaxis in leprosy was subject of a workshop held in Amsterdam and reported in 2007.[5] This workshop concluded that chemoprophylaxis may make a contribution to leprosy control but that a number of requirements needed to be

fulfilled. The publication of the Bangladesh trial led to the recommendation in the Enhanced Global Strategy for Leprosy[6] on the exploration of the use of chemoprophylaxis as a tool to prevent the occurrence of new leprosy cases among household contacts as a result of this finding. A further consultation on the subject in London in 2009[7] recommended pilot projects on implementing chemoprophylaxis under routine programme conditions are recommended to assess acceptability, cost-effectiveness, feasibility, and ethical issues.

Recommendations for further research

Further study of blanket chemoprophylaxis is merited, particularly in light of the increasing use of blanket approaches in tackling other Neglected Tropical Diseases.

Further research is recommended in improving the effectiveness of chemoprophylaxis through development of the regimen.

Pilot projects on implementing chemoprophylaxis under routine programme conditions are recommended to assess acceptability, cost-effectiveness, feasibility, and ethic issues.

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2. Early diagnosis of leprosy

Paul Saunderson

Summary

There are two new reviews of studies of early case-detection. One review shows that there is an increased risk of leprosy in contacts, but the definition of a contact needs to include both people in the same household and others, such as neighbours and social contacts. The other review shows that individual counselling of new cases can help in identifying other new cases, but there are so few good evaluations of general health education efforts that no statement about its effectiveness in promoting early case detection can be made with confidence.

Recent evidence

We identified two systematic reviews relating to early diagnosis.

Moet[1] reviews studies of risk factors in contacts for developing leprosy. Contacts of MB cases have an 8-fold increased risk, compared with non-contacts, while contacts of PB cases have only a slightly increased risk. A recent study in Indonesia showed that neighbours and social contacts also have an increased risk, so that up to 78% of new cases could be linked to a previously diagnosed leprosy patient. The relative risk for household contacts was 9·4, for next-door neighbours 4·0, and for the next house again, 1·6. Hereditary factors also appear to play a role, although this review found that information to quantify the risk is not yet available. Age is a risk factor with two peaks of high incidence, firstly in children under 14 years and secondly in older adults; males are at higher risk in most studies. Those who have leprosy, and who have a high bacterial load (in other words, are more multibacillary), have a higher chance of passing it on. This review also looked at immunological and molecular markers: the presence of anti-PGL-I antibodies increases the risk of getting leprosy as does being lepromin negative, where as BCG vaccination decreases the risk. However, these tests were not yet capable of identifying subjects with sub-clinical disease who would be at high risk of developing active leprosy.

This review concludes that targeted interventions should be aimed at close contacts both inside and outside the household, particularly when genetically related. Contacts of PB patients should also be included in such interventions. The quality of the evidence for this recommendation is grade 1, based on at least one randomized controlled trial.

The second review[2] searched for proven and potential interventions to reduce the delay in diagnosing leprosy. Very little published evidence was found and the focus was entirely on health education interventions aimed at patients, their family members and other key individuals, such as students and teachers. No studies addressed problems encountered by women. Four studies evaluated health education in communities, while two studies looked at counselling of individual patients; one study in Brazil found that a simple education programme with new patients was as effective as a contact survey in locating new cases.

The conclusion was that more work needs to be done to study and evaluate methods of promoting early case detection.

Recommendations for further research

The following are suggested as priorities for further research in this area:

1. Operational research on ways of identifying appropriate groups of contacts and then arranging for counselling, examination and treatment (when necessary), possibly in conjunction with chemoprophylaxis.
2. Further work on the development and assessment of immunological and molecular markers for infection with *M. leprae* and early disease. Note: this is already being pursued by various groups within the IDEAL consortium.
3. Further evaluation of health education activities, including those that are targeted at certain groups such as teachers or women.

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3. Chemotherapy

Etienne Declercq

Summary

Very little solid evidence has emerged since the ILA Technical Forum of 2002 permitting any recommendations for drastic changes in the WHO MDT regimens. U-MDT trials are under way, but several years of follow up will still be necessary before being able to draw firm conclusions. The bactericidal activity of fluoroquinolones against *M. leprae* has been further studied and confirms their possible role as part of future and more potent multidrug therapy regimens. There is still a need to continue research for new, shorter, possibly fully supervised, MDT regimens, based on the combination of highly bactericidal drugs.

Recent evidence

1. A COMMON REGIMEN FOR BOTH PB AND MB LEPROSY

The WHO Technical Advisory Group, at its third meeting, recommended that trials be launched for treating all leprosy patients, both PB and MB, with the MDT regimen for MB leprosy for a period of only six months.[1] A protocol for this uniform MDT regimen (U-MDT) was developed, and a multi-centric trial was started. The aim was to recruit 2,500 PB and 2,500 MB patients, but only 2,094 PB and 1,302 MB patients were enrolled. The follow-up period has been extended to eight years, from the initially planned five years. The end of the study is foreseen in 2015. It is to be noted that this is not a comparative study. Some other centres in various countries, like Brazil and Bangladesh, have also started U-MDT[2] controlled trials. The results of these studies are still awaited. One randomized controlled trial was done by the Department of Dermatology and Leprosy of Gandhi Hospital, Secunderabad, India,[3] comparing U-MDT with standard WHO MDT for PB and MB leprosy. It included 127 consecutive untreated leprosy patients, of whom 64 were followed up for a minimum of 18 months and a maximum of 24 months: 32 PB (18 in the study group and 14 in the control group) and 32 MB (10 in the study group and 22 in the control group). Results at 24 months suggested, for the PB patients, a better progressive improvement in the study group than in the control group, but the differences were not statistically significant. For the MB patients, in clinical improvement grades, good responses in the control group was 36, 45 and 77% at 12, 18 and 24 months whereas the study group did not have a single good response at 12 and 18 months. These differences were statistically significant at all times. Although the numbers of patients are limited, and the results of this trial should be confirmed in other studies, this tends to show that 6-month U-MDT is too short a regimen to treat MB leprosy adequately.

2. SINGLE DOSE ROM IN PB PATIENTS

Randomized controlled trials have been carried out to compare the efficacy of a combination of rifampicin 600 mg plus ofloxacin 400 mg plus minocycline 100 mg administered as a single dose with that of standard WHO-MDT-PB given for six months.[4] One of these trials

included 32 previously untreated, skin smear negative PB patients having 1 to 3 skin lesions and having no evidence of peripheral nerve trunk involvement. Patients were randomly divided into study and control groups and followed up for six months. There was no significant difference between both groups after 6 months, concerning the reduction in the mean clinical and histopathological scores. However, the conclusions that one can draw from this study are rather weak, due to the small sample size and the follow-up limited to six months. In another study,[5] 51 patients who had two to three skin lesions and no peripheral nerve trunk enlargement were enrolled, randomly allocated to study and control groups and followed up for 24 months. Although complete cure, defined as total disappearance of all the lesions, was more frequent with WHO-MDT than with ROM, both regimens were found effective. Here also the small sample size limits the strength of the observation.

3. NEW MDT REGIMENS

The bactericidal activity of fluoroquinolones against *M. leprae* has been further studied[6] and confirms their possible role as part of future and more potent multidrug therapy regimens.

Recommendations for further research

1. Follow-up of present studies of U-MDT must be ensured, in order to be able to draw firm conclusions on the possibility to reduce the duration of WHO MDT to six months for MB leprosy patients.
2. Additional data must be collected on relapse rates after the 12-month MDT regimen for MB leprosy.
3. Trials of new, shorter, possibly fully supervised, MDT regimens, based on the combination of highly bactericidal drugs such as rifapentin, moxyfloxacin, clarithromycin, minocycline, or others, should be launched.
4. New drugs or new regimens should be developed for patients with rifampicin resistance or those presenting signs of intolerance.

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4. Reactions

Diana Lockwood

Type 1 Reactions

Summary

The data on the treatment of nerve damage and T1R can be summarised

1. The optimum length of steroid treatment is not known, although some data shows that a longer course might be better but this was a study using non-standardised scales (20 weeks treatment is superior to 12 weeks in one study).
2. The optimum dose of steroids is not known although so far no studies have shown an advantage for higher doses. No studies have used a dose per weight regimen.
3. There is a 20–50% relapse rate after patients have received steroid treatments.
4. Standardised tools are needed to measure outcomes so that studies are comparable.
5. Second line drugs for the treatment of reactions for patients who do not respond to prednisolone are also needed.
6. HIV and leprosy co-infection often present with a T1R and the optimum management of this needs defining.

Recent Evidence on Type 1 Reactions

There have been two reviews of the effect of corticosteroid treatment on nerve damage and (Type 1 Reaction) T1R, a Cochrane review by van Veen[1] and a comprehensive review by Walker and Lockwood.[2] Both reviews highlight the paucity of good trials in this area. The Cochrane review[1] considered only 3 trials, one by Sundar Rao[3] which was a RCT comparing two different doses of steroids (starting dose 60 mg vs 30 mg) and two different durations (12 weeks vs 20 weeks) and two other trials which looked at the effectiveness of steroids in the treatment of old nerve damage[4] and mild nerve damage respectively.[5] The second review[2] compares the outcomes of patients treated in prospective randomised studies. Only three of these studies found a benefit for steroid treatment, the Marlowe study[6] which showed that 50% of patients improved. The Sundar Rao study[3] did not use a standardised measure for improvement but instead used a clinician driven decision to give additional corticosteroids and the relative risk of needing additional steroids was compared between the three regimens; the relative risk for needing additional corticosteroids was lower in the patients given a higher dose of steroids for a longer period of time.

These studies are difficult to compare because they have all used different entry criteria and different outcome measures, some used ballpoint pen to assess sensation, some used mono-filaments, other invalidated clinical scales[7,8] or no scales at all.[3] This highlights the need to develop and validate clinical scales for measuring the severity of leprosy reactions and some progress has been made towards this.[9]

Different doses and duration of steroid treatment have also been used, again making comparison difficult. Some studies[7] have used a 12 week course of prednisolone, others 16 weeks[4,5] and one used a 20 week regimen.[3]

One of the striking features of the treatment studies on T1R is the substantial relapse rate, viz when the patient needs more steroids. In some studies[3] these have been used as the outcome. In other studies[5] it can be seen that patients start to relapse soon after stopping steroids. These data suggest that there is a sub group of patients whose reactions and nerve damage is not adequately treated by prednisolone. They might have persistent inflammation, perhaps driven by a pro-inflammatory genotype. If genotyping could identify patients who are at risk of developing further reactions this would be a very useful piece of research.

Further evidence for a longer regimen producing better outcomes in patients comes from the high relapse rates where 42·4% patients needed extra prednisolone.[7] The Sundar Rao study[3] indicates that treatment for 20 weeks has a better outcome than 12 weeks. In the assessment of the treatment of leprosy reactions it is very noticeable that studies done with either a non-randomised format or not prospectively had a much better outcome than blinded studies.

Other data on related aspects of the treatment of nerve damage comes from the two Tripod studies; Tripod 3[4] showed that prednisolone is not superior to placebo when used to treat patients with nerve damage that has been present for more than 6 months. Furthermore in Tripod 3, 38 and 29% of patients in the prednisolone and placebo treatment groups required extra steroids. In the placebo group this was markedly earlier than in the prednisolone group, (although not significantly so, perhaps because of the small number of particiapnts) The Tripod 2 study[5] showed that using a more sensitive measure of nerve damage- a monofilament as an tool for triggering treatment did not results in better outcome.

Several studies have indicated that some nerve function impairment will improve without steroid therapy. This improvement may be spontaneous or attributable to MDT. The prospective BANDS cohort[10] included 69 individuals with NFI who should have received prednisolone but did not. In these patients 33% of involved motor nerves and 62% of affected sensory nerves had some degree of improvement at 12 months follow up. The AMFES cohort[11] included 141 individuals with NFI at the time of enrolment which had been present for longer than 6 months and so were not treated with steroids. Between a quarter and a third of nerves with this longstanding impairment fully improved during the long period of follow up.

Prophylaxis of reactions using prednisolone was addressed in a randomised trial using a daily dose of 20 mg prednisolone. Reactions were prevented whilst it was given over 16 weeks but patients then developed reactions and by 12 months the Kaplan- Meier survival curves for the treatment and placebo were not significantly different.[12] This suggest that prednisolone can prevent reactions for only a short time.

The evidence suggests that there is a subset of patients who are at risk of developing reactions and the key question is to identify these patients – perhaps by genetic studies or by the use of more sensitive tests of nerve function. These patients might be predisposed to have persistent inflammation.

Women are under-represented in the studies of the treatment of T1Rs and this is a cause for concern. Gender inequalities may be more significant in leprosy as it is a highly stigmatizing disease. All the prospective studies outlined in the Table 1 have recruited more men than women with rates of female recruitment varying from 13–36%.

None of the studies on treatment for T1R have done patient-based assessments of quality of life in relation to the treatments being tested and this is an important aspect that needs to be captured in future studies.

Table 1. Prospective randomised studies using steroids in Type 1 reactions and/or nerve function impairment

Country, Year and Type of study	Entry criteria	No.	Intervention	Outcome measures	Conclusion
Brazil (Garbino, Virmond Mda *et al.* 2008) Randomised, controlled	Type 1 reactions or ENL associated with ulnar neuropathy	21	Prednisone 120 mg daily initially compared with 60 mg daily initially for controls. Tapered variably.	Clinical Score and motor nerve conduction	Difficult to compare groups. Clinical Score was not validated. Both types of reaction analysed together. 'Significant improvement over time'
India (Rao, Sugamaran *et al.* 2006) Double-blind randomised controlled, parallel group	'Severe' Type 1 reactions	334	3 prednisolone regimes: 3·5 g over 5 months 2·31 g over 5 months 2·94 g over 3 months	Amount of extra prednisolone required	The 5 month regimes were equally effective and less additional prednisolone was required by these two groups than by the 3 month group
Nepal (Marlowe, Hawksworth *et al.* 2004) Randomised, controlled	Type 1 reactions skin or skin and nerve	40	12 weeks azathioprine and 8 weeks prednisolone compared to 12 weeks prednisolone alone	Skin signs, nerve tenderness, sensory and motor testing and amount of extra prednisolone required	Equally effective
Nepal, Bangladesh (Richardus, Withington *et al.* 2003) Randomised placebo controlled, double blind	NFI of 6–24 months duration.	92	16 week standard prednisolone regime	Sensory and motor test scores	No difference
Nepal, Bangladesh (Van Brakel, Anderson *et al.* 2003) Randomised placebo controlled, double blind	Isolated mild sensory impairment	75	16 week standard prednisolone regime	Improvement in monofilament scores.	No difference between treated and untreated groups.

Second line therapies are needed for several reasons, to treat patients who do not respond, for the management of patients with adverse effects from steroids and to reduce the relapse rate drugs. The use of second line drugs for patients who do respond to prednisolone has been addressed in two studies, one RCT comparing prednisolone alone versus prednisolone and azathioprine.[7] This study showed that the combination was as effective. A multi-centre study in India is currently comparing four regimens, prednisolone alone, prednisolone plus azathioprine for either 24, 36 or 48 weeks. The addition of azathioprine may reduce the relapse rate in T1R which is so problematic.

A study in Addis Ababa[6] in patients with T1R found that patients treated with a combination of Cyclosporin and prednisolone had similar outcomes (nerve function and skin signs) to published studies. A study in which patients with T1R and/or NFI will be randomised to receive either both cyclosporine and prednisolone or prednisolone alone is about to start.

Recommendations for further research

The important research questions are

1. Large studies are urgently needed to determine the optimum dose and duration of prednisolone treatment of nerve damage and T1R.
2. Large studies are also needed in Africa and Brazil because most of the data comes from the Indian sub-continent (India, Bangladesh and Nepal).
3. Standardised scales need to be used so that studies are comparable.
4. How can we identify the 20–50% of MB leprosy patients who develop reactions?
5. Can this be done by the use of more sensitive tests?
6. Can genotyping identify patients at risk of relapse?
7. Second-line treatments are needed for patients who do not respond to prednisolone.
8. HIV and leprosy - defining treatment regimens.

Type 2 (ENL Reaction)

Summary

1. There is a serious data gap with only 3 studies published recently on treatments for ENL.
2. Internationally recognised and validated severity scales need to be developed so that results from different countries can be compared.
3. A trial directly comparing prednisolone and thalidomide has never been done, and is urgently needed.
4. 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.
5. The development of a safe and effective alternative to both steroids and thalidomide is a high priority.

Recent Evidence on ENL Reaction

Two reviews[13,14] have highlighted the very poor quality of studies on ENL. These studies were done with very small numbers of patients, validated scales for measuring outcomes were not used and nearly all these studies were done 30–40 years ago, before the introduction of MDT and do not reflect contemporary practice. The Cochrane review[14] and identified 13 studies on treatments for ENL. These included studies on assessing betamethasone,[15] thalidomide,[16–19] pentoxifylline,[20] clofazimine,[21–23] indomethacin[24,25] and levamisole.[26] These were also too small to identify important clinical differences even if they existed. Three small trials showed benefit for thalidomide and clofazimine treatment in terms of fewer further reactions, more treatment successes, and fewer relapses of ENL.

Only two studies relating to the effect of Thalidomide in the treatment of ENL have been completed since the introduction of MDT.[19,20] The double blind randomised study of 22 patients[19] compared thalidomide 100 mg daily with 300 mg daily given for 1 week in patients with ENL. The patients receiving the lower dose then received 50 mg daily for 2 weeks followed by dummy capsules for 4 weeks. The group who initially received 300 mg of thalidomide was weaned down to zero over the following 6 weeks. There was no significant difference in the response of the two groups at the end of the first week of treatment with thalidomide. The lower dose group however experienced a statistically significant flaring of skin lesions during the 7-week treatment period indicating that the lower dose is less effective in maintaining the patient ENL free. Global assessment scores of symptom severity improved on thalidomide. The three individuals deemed to be treatment failures were all in the higher dosage arm of the study.

Sales[20] recruited 44 Brazilian patients with ENL into a double blind randomized controlled trial comparing pentoxifylline and thalidomide.46 Individuals with neuritis were excluded and follow-up was short at 30 days. Thalidomide was more effective than pentoxifylline but one can not be confident that ENL severity was similar in the two groups.

Second line drugs have been identified (cyclosporine, methotrexate, azathioprine, zafirlukast, infliximab) for which there is some evidence that they might be useful in the treatment of ENL but none has been assessed in-adequately powered studies using validated scales.[13]

None of these studies have assessed the impact of treatment on quality of life. The conclusion of the Cochrane reviewers that treatment with thalidomide was superior to acetylsalicylic acid (aspirin) (RR 2·43; 95% CI 1·28 to 4·59) (1 trial, 92 participants) with respect remission of skin lesions to). The conclusion that Clofazimine treatment was superior to prednisolone (more treatment successes; RR 3·67; 95% CI 1·36 to 9·91) (1 trial, 24 participants), and thalidomide (fewer recurrences RR0·08; 95%CI 0·01 to 0·56) (1 trial, 72 participants) is surprising and contradicts clinical experience which suggests that Thalidomide is superior to Prednisolone and clofazimine, especially in preventing recurrences.

Recommendations for further research

1. It is recommended that internationally recognised and validated severity scales be developed so that results from different countries can be compared.
2. A trial directly comparing prednisolone and thalidomide has never been done, and is urgently needed.

3. 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.
4. The development of a safe and effective alternative to both steroids and thalidomide.

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5. Prevention of Disability

Hugh Cross

Summary

The remit agreed by the ILEP Technical Commission was to consider research published since the International Leprosy Association (ILA) Technical Forum, 2002.[1] In September 2006 available evidence and reports of best practice of POD were reviewed at the Consensus Development Conference (CDC) which was convened in Cebu, The Philippines. The outcomes of the CDC were published in 2007,[2] this review, therefore, focuses primarily on POD developments and research findings published since the 2006 CDC.

Self-Care

Li *et al.* described the experience of implementing self-care in The Peoples Republic of China.[3,4] Earlier studies from China had indicated the status and effectiveness of self-care in other Chinese provincial programmes,[5–7] but the studies of Li *et al.* demonstrated that self-care implemented through the agency of government health workers was not only an effective intervention, but that it was also sustainable. After one year without any monitoring or supervision Li *et al.* found that over 80% of people who had been encouraged to do so had adhered to self-care practice.

Other studies since the CDC have demonstrated the efficacy of the intervention in NGO implemented programmes in India[8,9] and Nigeria.[10] Through these studies the importance of the roles assumed by self-care facilitators has been acknowledged and social support through the crucial early stages of behaviour change has been emphasised. The potential for significant effects, as indicated by ulcer healing and ulcer prevention rates, has also been well documented.

Even with the sound body of evidence to support the efficacy of self-care, the implementation of the intervention through national programmes remains a challenge. A survey conducted by the author ascertained that the implementation of POD globally was generally poor in low income countries whilst middle income countries have been able to implement essential POD activities to a better extent.

Footwear

Since the study of Seboka *et al.*[11,12] there has been a dearth of research regarding the efficacy of market footwear. A well designed study by Reiber *et al.* in 2002 did conclude that therapeutic footwear designed for people with diabetic neuropathy was not more effective than market footwear.[13] It should be noted that the population Reiber *et al.* studied was not characteristic of leprosy affected people in low resource environments. There have not been recent studies of the efficacy or cost effectiveness of market footwear for such populations.

In 2008 Cross and Lehman attempted to raise awareness of biomechanical risk factors associated with plantar ulceration in leprosy and have shown that appropriately trained technicians and therapists can identify such features.[14] This knowledge should allow the prescription of appropriate orthotic appliances which an early study showed to be an effective adjunct to footwear for ulcer healing.[15] The delivery of services required for the prescription and supply of orthotic appliances in low income countries, however, is probably limited to NGO programmes.

Wound Care

Forsetlund *et al.* undertook a systematic review of reports of ulcer interventions applied to people affected by leprosy and came to the salutary conclusion that '*reporting of both, methods and results suffered from underreporting and disorganization*'. They did acknowledge that the context in which leprosy complications are treated are problematic and that running high quality randomised controlled trials would be problematic.[16]

Bhatia *et al.* conducted a double blind randomised trial to compare the effects of diphenylhydantoin (DpH) (phenytoin) and normal saline as interventions for the treatment of simple ulcers in leprosy. They found that wounds treated with either 2% or 4% phenytoin suspension in normal saline had a significantly quicker healing rate than normal saline. They also reported other favourable indications: healthy granulation tissue appeared earlier in the intervention group and there was an earlier cessation of discharge.[17]

Carneiro and Nyawawa conducted a prospective randomized controlled study in a relatively low resource situation and compared phenytoin to Edinburgh University solution of lime (EUSOL). The primary outcome measure was the rate of ulcer healing, in non-malignant chronic leg ulcers. They found that compared with the EUSOL group, the phenytoin group showed significant reduction in the mean ulcer surface area on days 7, 14, 21 and 28 ($p < 0{\cdot}05$). They suggested that phenytoin powder is cheap, easily applied topically on ulcers, effectively relieves pain, clears discharge and enhances formation of granulation tissue thereby promoting healing. They advocate for its use since it reduces morbidity and the financial burden on resource-poor environments.[18] This call was echoed by Bhatia *et al.*[17]

Shaw *et al.* conducted a rigorous systematic review of topical phenytoin and concluded that studies investigating the effect of topical phenytoin on wound healing are of moderate methodological quality, and these suggest that there may be a positive effect on wound healing in a variety of wounds.[19]

Optimal concentrations of phenytoin have not yet been established neither has the best method of delivery. Bhatia *et al.* found no significant difference between 2% and 4% phenytoin but suggested that normal saline is a good solvent for phenytoin and that liquid suspension applied on gauze is better than direct application of powder because powder tends to form an eschar (also reported in other papers). In another paper Bhatia and Prakash suggest that bulk research-grade powder can be used, and is available in many countries.[20]

Nerve Decompression (Neurolysis)

van Veen *et al.* conducted a structured review to investigate the efficacy of neurolysis. They found that although there were 10 potentially relevant studies only two satisfied the quality

criteria they had set, and that those two studies were heterogeneous. There was therefore insufficient data for meta analysis, and consequently insufficient evidence to draw robust conclusions regarding the efficacy of neurolysis over medical treatment for nerve function impairment. They had considered other findings, many of which (non randomised studies) suggested that neurolysis was effective for pain and tenderness relief. They suggested that there is a need to try and identify factors that may predict favourable responses to neurolysis or that specific patient types or nerves that may respond favourably should be identified. They also expressed the hope that future RCTs would give greater consideration to non-clinical effects: costs and quality of life.[21]

Bone Density

Kanaji *et al.* conducted a randomised, double blind trial comparing risedronate with placebo. Risedronate is described as a second generation bisphosphonate. Bisphosphonates are thought to interfere with the synthesis of signalling molecules affecting cell structure and function and the survival of osteoclasts. They may also have a weak inhibitory effect on osteoblast apoptosis (programmed cell death). Kanaji *et al.* sought to test a hypotheses that risedronate would effectively arrest osteoclastic mediated bone resorption and actively increase bone density. They established that oral administration of risedronate does significantly increase lumbar bone mass density. Oral administration of placebo did not achieve the same effects. They also ascertained that risedronate treatment was more effective to prevent incident vertebral fractures than treatment with oral administration of placebo.[22]

The author suggests that the significance of the research may have much wider application; it justifies further investigation of the potential of risedronate to arrest and even reverse the affects of neurological bone disorganisation, a far more common complication for leprosy affected people.

Jostel and Jude conducted a review of the medical treatment of Charcot neuroosteoarthropathy amongst people with diabetes mellitus and cited randomised trials that support the efficacy of bisphosphonates as agents that inhibit excess osteoclastic activation and suppresses proinflammatory cytokine response. They conceded that evidence is still required to establish ideal dosage and long term outcomes, but suggested that improved symptom control, decline in foot temperature, and a significant increase in bone turnover markers are sufficient indication for greater scrutiny of bisphosphonates as an adjunctive pharmacological therapy for Charcot neuroosteoarthropathy.[23]

The neurological bone disorganisation more commonly associated with leprosy shares most of the same features that describe Charcot neuroosteoarthropathy. The author suggests that a systematic review of bisphosphonate studies should be undertaken as an initial step to establish whether further investigation would be useful.

Further Perspectives on Developing POD

van Veen *et al.* opined that to achieve universal POD of adequate quality and coverage, it will be imperative that POD interventions are cost effective. They conducted the only systematic review of the cost effectiveness of POD related to leprosy that has been published, but their study confirmed that evidence for cost-effectiveness of POD is very scarce. Although an

initial search suggested there were 62 potential studies that might have been analysed, subsequent filtering through their quality criteria reduced the number to only three studies. Of the three studies they did identify two were small, single-centre randomised controlled trials and one was a model-based review. van Veen *et al.* conceded, therefore, that generalizability was limited. They suggested that issues including cost perspective of analysis, relevant and accurate costs, analysis of uncertainty in estimates, and issues of availability, affordability and sustainability should be addressed in cost effectiveness studies, but that these were inadequately reported or addressed in the studies found.[24]

Requirements for further Research

Self Care
- Health Systems Research in low income countries is required to establish what constitutes 'adequate resources' for implementing self-care and how they can be used to optimal effect.

Footwear
- A randomised control trial comparing force attenuating properties of materials commonly used for commercial footwear production should be undertaken.

Wound Care
- Optimal concentrations of topical sodium diphenylhydantoin (DpH) (phenytoin) as a treatment for wound care should be ascertained.
- The cost effectiveness of diphenylhydantoin (DpH) (phenytoin) as wound care agent should be established.

Bone Density
- Evidence is required to establish the ideal dosage and long term outcomes from the use of bisphosphonates as an adjunctive pharmacological therapy for neurological bone disorganisation.
- The cost effectiveness and efficiency of Residronate should be established.

Neurolysis
- Random control trials are still required to establish the efficacy of neurolysis.
- Factors that might predict favourable responses to neurolysis should be identified: e.g. are there specific patient types or nerves that may respond favourably?
- The effect that neurolysis may have on the quality of life for those who undergo such treatment should be established.

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6. Review of recent literature on leprosy and stigma

Wim H. van Brakel, Valsa Augustine, Bassey Ebenso & Hugh Cross

Summary

This review focussed mainly on measurement of stigma and interventions to reduce stigma in the more direct leprosy-related literature. Only papers of which the full-length article was available, and that contained either reviews or reports on original research, were included. We included 3 systematic reviews and 9 other articles drawing on studies in Nigeria, Nepal, India, Bangladesh, Indonesia and Brazil. In addition, we used 4 as yet unpublished studies on stigma.

The main findings can be summarised as follows:

1. Leprosy-related stigma is still a widespread problem in many endemic countries. Stigma is nowadays seen as a social process that is dynamic and context-dependent. However, there is evidence that the impact of stigma is remarkably similar in different countries and health conditions, despite enormous cultural diversity and differences in determinants.
2. Much can be learned from other disciplines working with stigmatised conditions, such as mental health and HIV/AIDS.
3. Many instruments are now available for measuring different aspects of stigma or the impact of stigma. There is a need to cross-validate these in the field of leprosy and in different cultural settings and to compare instruments to determinants which ones are the most suitable for a particular purpose.
4. Interventions against stigma should be used in combination and at various levels. Many potential strategies and interventions are available, but evidence of effectiveness is still very scarce, especially in the field of leprosy.
5. There is a need to use new approaches to the study of stigma, including disability studies, sociological, historical and emancipatory/participatory methods.

Recent evidence

No less than 56 papers were published between 2003 and 2009 addressing leprosy-related stigma. Of these, 37 were either reviews on stigma or reports from actual stigma-related studies. This review focussed mainly on measurement of stigma and interventions to reduce stigma in the more direct leprosy-related literature. Altogether, we have included 3 systematic reviews and 9 other articles drawing on studies in Nigeria, Nepal, India, Bangladesh, Indonesia and Brazil. In addition, we used 4 as yet unpublished studies on stigma; two studies on measurement from India and Indonesia, one recent annotated bibliography on leprosy and stigma[1], and an as yet unpublished review on 'Leprosy, Stigma and Disability' by Beatriz Miranda, which has just been completed under the umbrella of TEG contributions. The criteria of the Centre for Evidence Based Medicine (CEBM) were

[1]Available from: www.ilep.org.uk/library-resources/infolep-information-services/subjectguides/leprosy-related-stigma/

used for grading levels of evidence and subsequently making recommendations is used to give readers further perspective on the strength of evidence cited.

The first review[1] was conducted to examine work done on measuring stigma related to leprosy. References were obtained through a PubMed (Medline) search and through examining relevant bibliographies. The studies reviewed indicate that leprosy stigma is a global phenomenon, occurring in both endemic and non-endemic countries. The consequences of stigma affect individuals as well as the effectiveness of leprosy control activities. Despite enormous cultural diversity, the areas of life affected are remarkably similar. They include mobility, interpersonal relationships, marriage, employment, leisure activities, and attendance at social and religious functions. This suggests that development of a standard stigma scale for leprosy may be possible. Data obtained with such an instrument would useful in situational analysis, advocacy work, monitoring and evaluation of interventions against stigma, and for research to better understand stigma and its determinants.

Withington[2] investigated the relationship between socioeconomic factors and stigma in a cohort of 2,364 leprosy patients. One month after diagnosis, 2.1% indicated being affected by stigma. Smear positivity, female sex, and the presence of dependents were associated with an increase in the experience of stigma. The authors recommended an increased focus by leprosy services on the socio-economic factors associated with poorer physical and social outcomes.

A generic instrument to measure the impact of stigma (and other factors) on social participation was developed by the Participation Scale Development Group.[3] 2006). The Participation Scale (P-scale) measures participation according to the conceptual framework of the International Classification of Functioning, Disability and Health.[4] The P-scale was found to be reliable and valid to measure client-perceived participation in people affected by leprosy or disability in 6 different language areas in Nepal, India and Brazil. The P-scale has been translated in over 20 languages and is used in leprosy and in a variety of other disciplines, including HIV and general rehabilitation. The instrument was used in the Stigma Elimination Project (STEP) in Eastern Nepal to help evaluate the impact of the project.[5] The STEP Project had trained leprosy-affected persons as change agents in their own communities. Within 3 years from the start of the project, major changes had occurred and perceived social participation among the leprosy-affected persons in the project area was better than could be expected in the general population.

Barkataki[6] designed their own questionnaire to investigate knowledge and attitudes to leprosy among people affected and community members in Uttar Pradesh, North India. Unfortunately, the questionnaire itself was not published, nor any data about validation results or psychometric properties. The authors report disappointingly low awareness regarding leprosy and a perception that leprosy was still stigmatised and led to discrimination and restriction in social participation; this despite 'massive health education and IEC campaigns'.

Heijnders & van der Meij[7] conducted a review of scientific literature concerning stigmatised conditions to identify the different strategies and interventions that have been used in the field of leprosy, HIV/AIDS, TB, mental illness and epilepsy. They identified several levels at which interventions and strategies should be implemented. These are the intrapersonal, interpersonal, organizational/institutional, community, and the governmental/ structural level. The authors state that, 'Although a lot of work has been carried out on stigma and stigma reduction, far less work has been done on assessing the effectiveness of stigma-reduction strategies.' Hardly any randomised controlled trials on stigma reduction were

found. Unfortunately, the authors did not grade the evidence from the papers reviewed systematically. The strategies claimed to be effective mainly concentrated on the individual and the community level. According to Heijnders & van der Meij, to reduce health-related stigma significantly, single-level and single-target group approaches are not enough. A patient-centred approach is required, 'starting with interventions targeting the intrapersonal level to empower affected persons to assist in the development and implementation of stigma-reduction programmes at other levels.'

The following table on stigma reduction strategies has been adapted from Heijnders & van der Meij[7]:

Intervention level	Strategies
Intrapersonal level	Treatment
	Counselling
	Cognitive-behavioural therapy
	Empowerment
	Group counselling
	Self-help, advocacy, support groups
Interpersonal level	Care and support
	Home care teams
	Community-based rehabilitation
Organisational/institutional level	Training programmes
	(New) policies, like patient-centred and integrated approaches
Community level	Education
	Contact
	Advocacy
	Protest
Governmental/structural level	Legal and policy interventions
	Rights-based approaches

The authors suggested two major points for consideration. First, stigma is a social construct and not an attribute of individuals. Therefore, we must not expect the persons affected alone to carry the burden of activism against stigma or that educating the general public and increasing their tolerance is enough. Second, persons affected are not passive agents in the stigma-reduction process. Several studies found that they can take an active role in stigma reduction interventions, and that programmes should be more person-centred. 'These constructs lead us to believe that interventions should aim first at empowering affected persons, always taking note of the context in which they find themselves. Persons who are empowered and are aware of the barriers to active community participation and their human rights can set the priorities regarding the need for institutional and national change. Studies showed that a combination of counselling, education and contact are very promising. Broad interventions at the governmental level need to support these efforts and create a shift in the power relations that otherwise remain in position and allow stigma to continue.'

Van Brakel[8] reviewed 63 published papers and 5 unpublished studies presenting or using instruments to measure stigma in the fields of HIV/AIDS, leprosy, tuberculosis, mental health, epilepsy and a number of other health conditions. Available psychometric property figures were not presented for each instrument, nor was evidence grading performed based on such parameters. One of the main conclusions was that '. . .the impact of stigma is remarkably similar in different countries and health conditions, despite enormous cultural diversity and differences in determinants.' Because of the similarity in the consequences of

stigma in different cultures, and the apparent cross-cutting applicability of many items from stigma instruments, the author suggested that it would be possible to develop a generic set of stigma assessment instruments. Aspects of stigma that were proposed for measurement were public attitudes, discriminatory or stigmatising practices (including legislation, structural discrimination and media), experience of discrimination and participation restrictions among affected people, perceived (or felt) stigma, and internalised (or self) stigma. Several instruments with potential for cross-cultural or cross-disciplinary validation were identified. A toolkit of such instruments was validated for use with leprosy affected persons in the recent SARI study in India.

Weiss[9] suggested a new definition of health-related stigma, 'Stigma is typically a social process, experienced or anticipated, characterized by exclusion, rejection, blame, or devaluation that result from experience, perception, or reasonable anticipation of an adverse social judgment about a person or group. This judgment is based on an enduring feature of identity conferred by a health problem or health-related condition, and the judgment is in some essential way medically unwarranted.'.[9] The definition emphasises the dynamic and experiential nature of stigma. In a more recent paper, Weiss proposed an expansion of Scambler's 'Hidden distress model' of stigma as a conceptual framework for stigma interventions.[10]

Stigma, quality of life and mental health among persons affected by leprosy in Bangladesh was investigated in a series of studies.[11–13] They found that perceived stigma was strongly associated with reduced quality of life and concluded that 'there is an urgent need for interventions sensitive to the effects of perceived stigma, gender, and medical conditions to improve the QOL and mental health of Bangladeshi leprosy patients.'

Raju[14] conducted a large community study on leprosy-related stigma in several states in North India. They developed their own stigma measurement scale, which was not published along with the paper, not were any psychometric properties reported. A baseline survey confirmed a high level of stigma. Some innovative interventions were suggested by community representatives themselves, such as initiating 'stigma reduction organizing committees in each village'. Education and counselling are offered through these committees. The initial experiences have been very positive, but a formal evaluation of the impact is yet to be published.

A summary of several in-depth studies on gender and leprosy in Indonesia, Nigeria, Nepal and Brazil was published by Varkevisser.[15] Though not focussing specifically on this, stigma was a recurring theme and reason for under-reporting of women in these societies. The authors state that 'accessible, well-reputed services augmented female participation and helped to diminish stigma, which in three out of the four societies seemed greater for women than for men. These positive effects could still be higher if the services would enhance community and patient education with active participation of patients and ex-patients themselves.'

Schuller conducted a study in South Sulawesi, Indonesia, to validate a toolkit for Rapid Disability Appraisal among people with leprosy-related and other disabilities.[16] As part of this study, they compared the experience of disability and the impact of stigma between women with leprosy-related disability and women with other disabilities. Key informants reported that people with disabilities not caused by leprosy were generally treated well by the community; they were respected and not avoided. However, all women with disabilities gave evidence of the existence of stigma, resulting in social participation restrictions. Women affected by leprosy were especially stigmatised by relatives and community members.

They also suffered from self-stigma. Disabilities and stigma resulted in lower education, income and marriage prospects for all women.

An unusual contribution is made by the paper 'Leprosy, stigma and disability – What has been done and what could be done: taking advantage of theory and practice' by Beatriz Miranda.[17] This paper was commissioned as part of the wider TEG work on stigma. Rather than presenting a review of already familiar literature, Miranda draws on literature and own expertise in the field of disability studies, social sciences and historical studies to present a well-written and very refreshing critique of the way we tend to look at leprosy and leprosy-related stigma. She argues that the way society, professionals and also leprosy experts look at leprosy and particularly leprosy-affected persons does not do justice to their situation. This is because it usually disregards historical influences and powerful social, cultural political and structural forces that influence the way leprosy is seen in society and the way affected people are treated (in the widest sense of the word).

'Whilst health and medical issues are of course involved, the question is how to make a critical combination between scientific and social research that underestimates neither the characteristics of the disease nor the structural problems affecting the individuals. . .'.

'We are arguing for an approach that looks to understand the lives of people with Hansen's disease in culturally and historically specific terms, acknowledges strategies of resistance developed as well as suffering and discrimination, and that (above all) insists on the need to empower its subjects through enabling their active participation.'

'[There is] A need to reposition leprosy in the light of developments in the Social Sciences and the experience of Disability Studies is a major conclusion of this review: a repositioning which would have an effect on its political treatment.'

These few quotes indicate the fairly radical 'paradigm shift' advocated in Miranda's paper.[2] This should give new food for thought – and hopefully concerted action – to those involved in leprosy services and, particularly, leprosy research.

Recommendations for future research

1. Future research on leprosy-related stigma should take multiple perspectives into account with regard to the process of stigmatisation. This should include cultural, religious, historic and structural/political perspectives.
2. Every effort should be made to include persons affected by leprosy in stigma-related research. Emancipatory research should be encouraged in which affected persons take the lead in investigations and in which their specific and unique contributions are acknowledged.
3. Randomised controlled trials are needed of stigma reduction interventions and of various approaches to counselling.
4. There is a need for systematic reviews that take a critical look at published evidence, grading it according to recognised scientific standards.
5. Lessons should be learnt from stigma research outside the field of leprosy, such as HIV/AIDS and mental health.
6. Validation studies should be conducted to test the psychometric properties of stigma measurement instruments, also when instruments are introduced in new cultural or language settings.

7. Comparative studies should be conducted to determine the optimal instruments for measuring particular aspects of stigma.

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7. Review of New Evidence on 'Leprosy Rehabilitation'

Sunil Deepak

Summary

A literature review was conducted on recent systematic research studies and other relevant publications related to 'Rehabilitation of Persons affected with leprosy'. The review provided evidence for wider application of community-based rehabilitation and self care strategies.

The review also looked at new or emerging areas related to rehabilitation that merit research. Issues of providing rehabilitation services in integrated settings, implementing human rights approach related to the new 'UN Convention on Rights of Persons with Disability' and involvement of organisations of affected persons in planning and implementation of rehabilitation strategies, were identified as areas that require future research.

New Evidence

One systematic review on the theme of rehabilitation was identified. There were no published or on-going controlled trials related to rehabilitation of persons with disabilities due to leprosy. A number of additional papers and documents were also reviewed. The documents analysed and the issues identified are as follows:

Systematic Review: Evidence for the effectiveness of rehabilitation-in-the-community programmes[1]: rehabilitation-in-community programmes are effective in increasing independence, mobility & communication skills of persons with disabilities, helped parents of disabled children to cope better, helped children to attend school, some increase in incomes. The review concluded that rehabilitation in the community programmes are most useful to persons with mild disabilities.

> *All studies showed that high percentage of clients learned new skills or were able to perform activities of daily living they had not been able to before, gained more mobility or autonomy. Percentages of clients who reported improvements were 50% or higher and exceeded 75% in 5 out of 12 reports.*

Other research and significant documents

1. The WHO publication, Innovative Care for Chronic Conditions,[2] examined the organisation of health services for chronic conditions, including disability and rehabilitation services, and concluded that health services continue to be organised according to the 'acute episodic model of care' that governed the setting up health services that previously governed. It proposed a different paradigm for organising health services for persons with chronic conditions, often requiring life long care:

Chronic conditions require that patients make lifestyle adjustments to manage their problems. Lifestyles do not change with a medication. . . emphasis must be upon the patient's role and responsibility in health care. Focusing on the patient in this way constitutes a dramatic modification in current clinical practice. At present, systems relegate the patient to the role of passive recipient of care, missing the opportunity to leverage what he or she can do to promote personal health. Health care for chronic conditions must be reoriented around the patient.

2. Another WHO publication, Community-Based Rehabilitation As We Have Experienced It . . . Voices of Persons with Disabilities[3] looked at impact of community-based rehabilitation (CBR) programmes in three countries. Impact assessment was carried out through qualitative methods (interviews, case studies and focus group discussions) by a team of researchers with personal experiences of disabilities. The research concluded that CBR programmes can be effective in promoting empowerment, self-esteem, social acceptance and autonomy of persons with disabilities.

3. Development and trends in rehabilitation in leprosy[4] and the principles governing effective rehabilitation services

   Three general principles are identified. First, programmes must be responsive to the broad impact of the disease – physical, psychological, social and economic. Second, for effective rehabilitation the response must be specific to the needs and concerns of each individual. Third, the concerns and priorities of families and communities must influence decision-making.

4. Integrating community-based rehabilitation and leprosy rehabilitation services into an inclusive development approach[5]:

   Both CBR and, to a lesser extent, leprosy rehabilitation services, position themselves within a human rights approach and consequently state that rehabilitation services should support people with disabilities to access and exert their rights. The key issue here is 'inclusive development' meaning that rehabilitation services should aim at including people with disabilities in mainstream development programmes and strategies.

   There is a definite need for a mid level cadre that supports people with disabilities at community level. This support should primarily aim at involving people with disabilities in all types of community activities and especially in activities set up to improve the livelihood of the community members.

5. U.N. Convention on Rights of Persons with disabilities (UNCRPD): The UN Convention on Rights of Persons with Disabilities[6] was approved in December 2008 and at the end of 2009, has been signed by 78 countries. Many articles of the Convention have a direct bearing on rehabilitation services. At the same time, CRPD asks for 'human rights approach'. Some of the recommendations of the articles of the Convention that relate to rehabilitation needs of persons with disabilities due to leprosy are as follows:

Countries must protect the physical and mental integrity of persons with disabilities, just as for everyone else (Article 17), guarantee freedom from torture and from cruel, inhuman or degrading treatment or punishment, and prohibit medical or scientific experiments without the consent of the person concerned (Article 15).

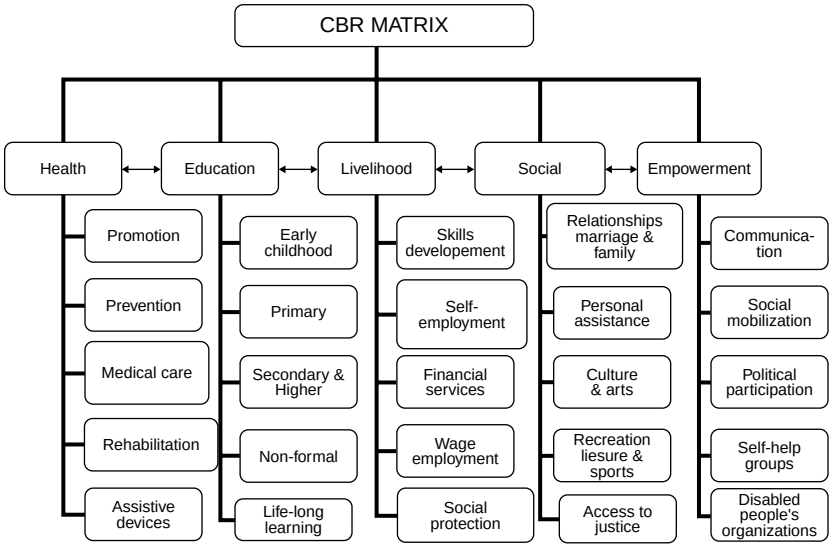
On the fundamental issue of accessibility (Article 9), the Convention requires countries to identify and eliminate obstacles and barriers and ensure that persons with disabilities can access their environment, transportation, public facilities and services, and information and communications technologies.

Personal mobility and independence are to be fostered by facilitating affordable personal mobility, training in mobility skills and access to mobility aids, devices, assistive technologies and live assistance (Article 20).

To enable persons with disabilities to attain maximum independence and ability, countries are to provide comprehensive habilitation and rehabilitation services in the areas of health, employment and education (Article 26).

6. CBR Matrix[7] proposed by WHO, provides a visual representation of CBR and proposes a standardised format for organising activities under five sectors or components – health, education, livelihood, social and empowerment. Each component is further made of specific elements.

It is a 'pick and mix' series of options, a set of components and elements from which the practitioner can select. Any one programme may choose to address only some of the components and elements. The matrix should not be seen as sequential. At the same time, the implementer needs to be in touch with other key organisations that usually take care of other components/elements.



Recommendations

There is a need to further promote and build on involvement of persons affected by leprosy in all aspects of their care and rehabilitation with emphasis on CBR and on holistic view of rehabilitation needs (EB).

Areas that should be recommended for action but which also require research include:

- Rehabilitation activities can be organised and monitored in terms of the CBR matrix, for ensuring that all the different needs of persons affected with leprosy are considered, including self-care and socio-economic rehabilitation (BP).
- Understanding principles and practices of a 'human rights approach' in practical implementation of rehabilitation activities in the field conditions (BP).
- Defining the components of 'holistic' approaches towards rehabilitation including self-care, footwear and mobility aids, SER, education, advocacy and lobbying for rights and services. Role of persons affected by leprosy and their organisations in all aspects of their care and rehabilitation requires a specific focus (R).

Many of these issues have been already raised in recent documents including the Global Strategy for leprosy control 2011–2015, in publications like Technical guidelines on CBR[8] and the upcoming module on 'Leprosy and CBR' in the new WHO CBR Guidelines.

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[5] Finkenflugel H, Rule S. Integrating community-based rehabilitation and leprosy rehabilitation services into an inclusive development approach. *Lep Rev*, 2008; **79**: 83–91.
[6] U.N. Convention on Rights of Persons with disabilities (UNCRPD), United Nations, New York, 2008.
[7] CBR Matrix www.who.int/disabilities/cbr/matrix/en/index.html consulted on 29 May 2010.
[8] WHO/ILEP Technical guidelines on CBR, ILEP London 2008.

Contributors

Contributorship

The literature search was planned and conducted by Jenny Batty during 2009 under the supervision of Cairns Smith. Lenka Nahodilova (ILEP) and Jiske Erlings (Infolep) assisted with the review and in accessing the key journal articles. The published evidence for each section was reviewed and the sections written as follows: Prevention – Immunoprophylaxis (Saunderson) and chemoprophylaxis (Smith), Diagnosis (Saunderson), Chemotherapy (Declercq), Reactions (Lockwood), Prevention of disability (Cross), Stigma (van Brakel assisted by Valsa Augustine, Bassey Ebenso and Hugh Cross), and Rehabilitation (Deepak). The draft document was then presented and discussed at a Forum held in London in March 2010. The document was then revised and the final document approved by all members of the ITC in May 2010.

Tribute

The ITC wish to pay tribute to Dr Augustin Guédénon who contributed, as a member of the ITC, to the planning and implementation of this review. Augustin died following a traffic accident in January 2010 in Abomey, Bénin. He made a quiet and thoughtful contribution to this work from his wealth of experience and knowledge, he will be missed.

The ITC also wish to pay tribute to Professor Ji Baohong who was a member of the ITC for many years and made an outstanding contribution in the field of leprosy chemotherapy. Ji died in Paris in February 2010.

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Table 1. Key Recent Evidence on Prevention of Leprosy

a. Immunoprophylaxis

Studies Reviewed	Level of evidence
1. Barreto ML, Pereira SM, Ferreira AA. BCG vaccine: efficacy and indications for vaccination and revaccination. *Jornal de Pediatria*, 2006; **82**: S45–S54.	1a
2. Setia MS, Steinmaus C, Ho CS, Rutherford GW. The role of BCG in prevention of leprosy: a meta-analysis. *Lancet Infect Dis*, 2006; **6**: 162–170.	1a
3. Zodpey SP. Protective effect of bacille Calmette Guerin (BCG) vaccine in the prevention of leprosy: a meta-analysis. *Indian J Dermatol Venereol Leprol*, 2007; **73**: 86–93.	1a
4. Rodrigues LC, Kerr-Pontes LRS, Frietas MVC, Barreto ML. Long-lasting BCG protection against leprosy. *Vaccine*, 2007; **25**: 6842–6844.	3b
5. Sharma P, Mukherjee R, Talwar GP, Sarathchandra KG, Walia R, Parida SK, Pandey RM, Rani R, Kar H, Mukherjee A, Katoch K, Benara SK, Tulsi & Singh P. Immunoprophylactic effects of the anti-leprosy Mw vaccine in household contacts of leprosy patients: clinical field trials with a follow up of 8–10 years. *Lepr Rev*, 2005; **76**: 127–143.	1b
6. Cunha SS, Alexander N, Barreto ML, Pereira ES, Dourado I, de Fátima Maroja M, Ichihara Y, Brito S, Pereira S, Rodrigues LC. BCG revaccination does not protect against leprosy in the Brazilian Amazon: a cluster randomised trial. *PLoS Negl Trop Dis*, 2008; **2**(2): e167.	1b
7. Düppre NC, Camacho LAB, da Cunha SS, Struchiner CJ, Sales AM, Nery JAC, Sarno EN. Effectiveness of BCG vaccination among leprosy contacts: a cohort study. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 2008; **102**: 631–638.	2b

b. Chemoprophylaxis

Studies Reviewed	Level of evidence
1. Oo KN, Yin NN, Han TT, Wai KT, Myint K, Gyi MM. Serological response to chemoprophylaxis in extended contacts in leprosy–a randomized controlled trial. *Japanese Journal of Leprosy*, 2008; **77**: 3–10.	1b
2. Saikawa K, Saikawa K. Study on prevention of leprosy. Chemo-prophylaxis trial for leprosy household contact children. *Japanese Journal of Leprosy*, 1985; **54**: 187–192.	2b
3. Bakker MI, Hatta M, Kwenang A, van Bentehem BHB, van Beers SM, Klatser PR, Oskam L. Prevention of leprosy using rifampicin as chemoprophylaxis. *American Journal of Tropical Medicine and Hygiene*, 2005; **72**: 443–448.	2b
4. Moet FJ, Pahan D, Oskam L, Richardus JH. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: Cluster randomised controlled trial. *BMJ*, 2008; **336**: 761–764.	1b
5. Oskam L, Bakker MI. Report of the workshop on the use of chemoprophylaxis in the control of leprosy held in Amsterdam, The Netherlands on 14 December 2006. *Leprosy Review*, 2007; **78**: 173–185.	5
6. World Health Organisation. Enhanced global strategy for further reducing the disease burden due to leprosy. 2011–2015 New Delhi, 2009.	5
7. World Health Organisation. Informal consultation on monitoring Grade-2 disability rate and applicability of chemoprophylaxis in leprosy control. London, November, 2009.	5

Table 2. Key Recent Evidence on Early Diagnosis of Leprosy

Systematic Reviews	Level of Evidence
1. Moet FJ, Meima A, Oskam L & Richardus JH. Risk factors for the development of clinical leprosy among contacts, and their relevance for targeted interventions. *Lepr Rev*, 2004; **75**: 310–326.	2a
2. Nicholls PG, Ross L & Smith WCS. Promoting early detection in leprosy – a literature review to identify proven and potential interventions addressing patient-related delay. *Lepr Rev*, 2006; **77**: 298–310.	3a

Table 3. Key Recent Evidence on Leprosy Chemotherapy
Levels of Evidence and Grades of Recommendation

Studies reviewed	Level of Evidence
Third Meeting of WHO Technical Advisory Group (TAG). Conclusions and recommendations.	5
Penna GO. Independent study to establish the efficacy of the six doses Uniform MDT regimen (U-MDT) for leprosy patients.	Ongoing trial
Narasimha Rao P, Suneetha S, Pratap DVS. Comparative study of Uniform-MDT and WHO MDT in Pauci and Multi bacillary leprosy patients over 24 months of observation. *Lepr Rev*, 2009; **80**: 143–155.	1b
Deshmukh AR, Dhurat RS, Jerajani UR. A comparative clinico-pathologica study of single-dose ROM in paucibacillary leprosy patients with 1–3 skin lesions. *Indian J Lepr*, 2003; **75**(3): 209–217.	1b
Emmanuel M, Gupte MD. Lesional characteristics and histopathology in paucibacillary leprosy patients with 2 or 3 skin lesions: comparison between ROM and PB-MDT regimens. *Indian J Lepr*, 2005; **77**(1): 19–25.	1b
Fajardo TT Jr, Villahermosa LG, Dela Cruz EC, Cellona RV, Balagon MAVF, Abalos RM, Gelber RH. A clinical trial of pefloxacin and ofloxacin in lepromatous leprosy. *Lepr Rev*, 2004; **75**: 389–397.	1b

Table 4. Key Recent Evidence on Leprosy Reactions

Systematic Reviews	Level of Evidence
1. Van Veen NH, Nicholls PG *et al.* Corticosteroids for treating nerve damage in leprosy. *Cochrane Database Syst Rev*, 2007; (2): CD005491.	1a
2. Walker SL, Lockwood DN. Leprosy type 1 (reversal) reactions and their management. *Lepr Rev*, 2008; **79**(4): 372–386.	2a
3. Walker SL, Waters MF *et al.* The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev*, 2007; **78**(3): 197–215.	2a
4. Van Veen NH, Lockwood DN *et al.* Interventions for erythema nodosum leprosum. *Cochrane Database Syst Rev*, 2009; (3): CD006949.	1a
Randomised controlled trials	**Level of Evidence**
Garbino JA, Mda CV *et al.* A randomized clinical trial of oral steroids for ulnar neuropathy in type 1 and type 2 leprosy reactions. *Arq Neuropsiquiatr*, 2008; **66**(4): 861–867.	1b
Rao PS, Sugamaran DS *et al.* Multi-centre, double blind, randomized trial of three steroid regimens in the treatment of type-1 reactions in leprosy. *Lepr Rev*, 2006; **77**(1): 25–33.	1b
Marlowe SN, Hawksworth RA *et al.* Clinical outcomes in a randomized controlled study comparing azathioprine and prednisolone versus prednisolone alone in the treatment of severe leprosy type 1 reactions in Nepal. *Trans R Soc Trop Med Hyg*, 2004; **98**(10): 602–609.	1b
Richardus JH, Withington SG *et al.* Treatment with corticosteroids of long-standing nerve function impairment in leprosy: a randomized controlled trial (TRIPOD 3). *Lepr Rev*, 2003; **74**(4): 311–318.	1b

Table 5. Key Recent Evidence on Prevention of Disability in Leprosy
Levels of Evidence and Strength of Recommendation

Studies Reviewed	Level of Evidence
Li J, Mu H, Ke W *et al.* The sustainability of self-care in two counties of Guizhou Province, Peoples' Republic of China. *Lepr Rev*, 2008; **79**(1): 110–117.	4
Ebenso J, Muyiwa LT, Ebenso BE. Self care groups and ulcer prevention in Okegbala, Nigeria. *Lepr Rev*, 2009; **80**(2): 187–196.	4
Madhavan K, Vijayakumaran P, Ramachandran L *et al.* Sustainable leprosy related disability care within integrated general health services: findings from Salem District, India. *Lepr Rev*, 2007; **78**(4): 353–361.	2b
Chakraborty A, Mahato M, Rao PS. Self-care programme to prevent leprosy-related problems in a leprosy colony in Champa, Chattisgarh. *Indian J Lepr*, 2006; **78**(4): 319–327.	2b
Reiber GE, Smith DG, Wallace C *et al.* Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. *JAMA*, 2002; **287**(19): 2552–2558.	1b
Boulton AJ, Jude EB. Therapeutic footwear in diabetes: the good, the bad, and the ugly? *Diabetes Care*, 2004; **27**(7): 1832–1833.	5
Cross HA, Lehman L. The validity and reliability of a simple semantic classification of foot posture. *Lepr Rev*, 2008; **79**(4): 416–424.	3b
van Veen NH, McNamee P, Richardus JH, Smith WC. Cost-effectiveness of interventions to prevent disability in leprosy: a systematic review. *PLoS One*, 2009; **4**(2): e4548.	1a
Forsetlund L, Reinar LM. Quality of reporting and of methodology of studies on interventions for trophic ulcers in leprosy: A systematic review. *Indian Journal of Dermatology, Venereology and Leprology*, 2008; **74**(4): 331–337.	1a
Bhatia ANSGSaRBS. Topical phenytoin suspension and normal saline in the treatment of leprosy trophic ulcers: a randomized double blind comparative study. *The Journal of Dermatological Treatment*, 2004; **15**(5): 321–327.	1b
Carneiro PM, Nyawawa ET. Topical phenytoin versus EUSOL in the treatment of non-malignant chronic leg ulcers. *East Afr Med J*, 2003; **80**(3): 124–129.	2b
Shaw J, Hughes CM, Lagan KM, Bell PM. The clinical effect of topical phenytoin on wound healing: a systematic review. *Br J Dermatol*, 2007; **157**(5): 997–1004.	1a
Bhatia A, Prakash S. Topical phenytoin for wound healing. *Dermatol Online J*, 2004; **10**(1): 5	5
van Veen NH, Schreuders TA, Theuvenet WJ *et al.* Decompressive surgery for treating nerve damage in leprosy. A Cochrane review. *Lepr Rev*, 2009; **80**(1): 3–12.	1a
Kanaji A, Higashi M, Namisato M *et al.* Effects of risedronate on lumbar bone mineral density, bone resorption, and incidence of vertebral fracture in elderly male patients with leprosy. *Lepr Rev*, 2006; **77**(2): 147–153	1b
Jostel A, Jude EB. Medical treatment of Charcot neuroosteoarthropathy. *Clin Podiatr Med Surg*, 2008; **25**(1): 63-vii.	3a

Table 6. Key Recent Evidence on Leprosy Stigma
Level of evidence and strength of recommendations in the papers reviewed. The papers are listed in chronological order

Studies Reviewed	Level of Evidence
van Brakel WH. Measuring Leprosy Stigma – A Preliminary Review of the Leprosy Literature. *International Journal of Leprosy and Other Mycobacterial Diseases*, 2003; **71**(3): 190–197.	2a
Withington SG, Joha S, Baird D, Brink M, Brink J. Assessing socio-economic factors in relation to stigmatization, impairment status, and selection for socio-economic rehabilitation: A 1-year cohort of new leprosy cases in north Bangladesh. *Leprosy Review*, 2003; **74**(2): 120–132.	2b
Cross H, Choudhary R. STEP: An intervention to address the issue of stigma related to leprosy in southern Nepal. *Leprosy Review*, 2005; **76**(4): 316–324.	2c
Barkataki P, Kumar S, Rao PSS. Knowledge of and attitudes to leprosy among patients and community members: A comparative study in Uttar Pradesh, India. *Leprosy Review*, 2006; **77**(1): 62–68.	3b
Heijnders M, Van Der Meij S. The fight against stigma: an overview of stigma-reduction strategies and interventions. *Psychology, health & medicine*, 2006; **11**(3): 353–363.	2a
van Brakel WH. Measuring health-related stigma–a literature review. *Psychology, health & medicine*, 2006; **11**(3): 307–334.	2a
van Brakel WH, Anderson AM, Mutatkar RK, Bakirtzief Z, Nicholls PG, Raju MS, Das-Pattanayak RK. The Participation Scale: Measuring a key concept in public health. *Disability and Rehabilitation*, 2006; **28**(4): 193–203.	2c
Weiss MG, Ramakrishna J, Somma D. Health-related stigma: Rethinking concepts and interventions. *Psychology, Health and Medicine*, 2006; **11**(3): 277–287.	5
Tsutsumi A, Izutsu T, Md Islam A, Maksuda AN, Kato H, Wakai S. The quality of life, mental health, and perceived stigma of leprosy patients in Bangladesh. *Social Science and Medicine*, 2007; **64**(12): 2443–2453.	2b
Weiss MG. Stigma and the social burden of neglected tropical diseases. *PLoS Negl Trop Dis*, 2008; **2**(5): e237.	5
Raju MS, Rao PS, Mutatkar RK. A study on community-based approaches to reduce leprosy stigma in India. *Indian Journal of Leprosy*, 2008; **80**(3): 267–273.	2b
Varkevisser CM, Lever P, Alubo O, Burathoki K, Idawani C, Moreira TMA, Patrobas P, Yulizar M. Gender and leprosy: Case studies in Indonesia, Nigeria, Nepal and Brazil. *Leprosy Review*, 2009; **80**(1): 65–76.	3b
Schuller I, Van Brakel WH, Van Der Vliet I, Beise K, Wardhani L, Silwana S, Van Elteren, M, Hasibuan Y, Asapa AS. The way women experience disabilities and especially disabilities related to leprosy in rural areas in South Sulawesi, Indonesia. *Asia Pacific Disability Rehabilitation Journal*, 2010; **21**(1): 60–70.	2b

Table 7. Key Recent Evidence on Community Based Rehabilitation in Leprosy

Publications Reviewed	Level of Evidence
Velema JP, Ebenso B, Fuzikawa PL. Evidence for the effectiveness of rehabilitation-in-the-community programmes. *Lep Rev*, 2008; **79**: 65–82.	3a
Finkenflugel, Rule. Integrating community-based rehabilitation and leprosy rehabilitation services into an inclusive development approach. *Lep Rev*, 2008; **79**: 83–91.	5
Nicholls, Smith. Development and trends in rehabilitation in leprosy APDRJ, Selected Readings, Jan. 2002.	5
U.N. Convention on Rights of Persons with disabilities UNCRPD.	5

Acronyms used in this document

ALERT	All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre
AMFES	ALERT MDT Field Evaluation Study
BANDS	Bangladesh Acute Nerve Damage Study
BP	Best Practice
EB	Evidence Based
ENL	Erythema Nodosum Leprosum
EUSOL	Edinburgh University solution of lime
CBR	Community Based Rehabilitation
CDC	Consensus Development Conference
CEBM	Centre for Evidence Based Medicine
CRPD	Convention on Rights of Persons with Disabilities
HHC	Household Contacts
IDEAL	Initiative for Diagnostic and Epidemiological Assays for Leprosy
IEC	Information Education Communication
ILA	International Leprosy Association
ILEP	International Federation of Anti-leprosy Associations
ITC	ILEP Technical Commission
MB	Multibacillary
MDT	Multiple Drug Therapy
Mw	Mycobacterium W
NFI	Nerve function impairment
NGO	Non-government Organisations
PB	Paucibacilllary
PGL-1	Phenolic Glycolipid-1
POD	Prevention of Disability
P-scale	Participation scale
QOL	Quality of Life
R	Research
RCT	Randomised Control Trial
ROM	Single dose treatment (comprising rifampicin, oflaxacine and minocycline)
SARI	Stigma Assessment and Reduction of Impact
SER	Socio-Economic Rehabilitation
STEP	Stigma Elimination Project
TAG	Technical Advisory Group
TEG	Temporary Expert Group
TRIPOD	Trials in Prevention of Disability
T1R	Type 1 Reaction
U-MDT	Uniform Multiple Drug Therapy
UNCRPD	United Nations Convention on Rights of Persons with Disabilities
WHO	World Health Organisation