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FUTURE RESEARCH NEEDS IN LEPROSY

Highlights of the Pre Congress Workshop No. 7 January 29th and 30th 2008; International Leprosy Congress, 2008 Hyderabad, India

About 25 experts participated in this workshop. Four main topics were considered: Epidemiology & Control, Diagnosis & Classification, Chemotherapy & Chemoprophylaxis, and Prevention of Disability Each of these topics was introduced by a Lead speaker and followed by at least one main discussant before general deliberation by all the participants(Vide Annexes 1 and 2).

The following research needs have been identified in the four key areas for consideration by stakeholders, research organizations and leprosy institutions as well as by all those concerned/affected by leprosy. There has been no intention to prioritise, but to formulate guidelines of possible research.

A) Epidemiology and Control of Leprosy

1. *Epidemiology of infection* – This remains a 'Holy Grail' for leprosy epidemiology and control. Right now we lack tools for detailed studies. If the IDEAL consortium comes up with something useful – this would be extremely important.[1–5]
2. *Role of nasal carriage in transmission* – More work is needed to confirm that the PCR signals really are *M. leprae* and, if so, to understand the dynamics – is carriage persistent, transient or recurrent and does it induce protective immunity. The implications of how it contributes to transmission and persistence and if it should be a target for control interventions need further study.[6,7]
3. *Identification of environmental and animal reservoirs of M. leprae* – There is much evidence that armadillos harbour *M. leprae*, but their contribution to infection and disease in humans is still not clear. In addition there are several reports of associations with water, and of *M. leprae* PCR signals in water.[8–15]
4. *Studies on* '*provocation*' *of leprosy (BCG and HAART)* – There is much evidence that either vaccination (BCG or Mw) or HAART can provoke clinical onset or reactions. Understanding the absolute risks and the immunological mechanisms, requires clinico-immuno-epidemiological studies.[16–20]
5. *What aspect of poverty influences leprosy?* – Many studies have shown that leprosy is associated with poverty, but just what aspect of the poverty complex is responsible for this (hygiene, nutrition, crowding, intercurrent infection etc.) remains unclear.

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6. *Accurate estimation of relapses and drug resistance* – There is little evidence as yet that relapses or drug resistance are important, but weakened leprosy control programmes will be associated with inadequate treatment, and there is a need to monitor disease recurrences.[21–23]
7. *Methods to improve Data quality* – All epidemiology and control research is dependent upon good data. There needs to be a concerted effort to insist upon transparency and quality in leprosy data collection at all levels. Interpretation of data should be straightforward and clear. Moreover, data from different regions might have to be interpreted differently.
8. *Methods of strengthening of referral centres* – in areas of diagnosis and advanced treatment.
9. *Identification of the needs of field workers.*

B) Diagnosis and Classification

Newer tests that require further research to prove them useful in leprosy:

1. *Serology* – Newer antigens that require further research are MMP-II (bacterioferritin) – which is also reactive in PB sera, 35KD protein, other glycolipids like PDIM and GPL and mycolic acids like TMM and TDM. Antigen detection (like Antigen 18) is another new area of research identified instead of antibody detection, as the sensitivity and specificity of serology may be improved.[24–27]
2. *Skin test antigens* – A new generation of skin test antigens which are more specific than existing ones, such as two new antigen preparations derived from Armadillo –derived *M. leprae* named MLSA-LAM and the second product, *M. leprae* cell wall antigen (MLCwA) need to be looked into.[28–30]
3. *Post genomic approach* to identify new diagnostic antigens – After the completion of genome sequencing of *M. leprae* in 2000, genes that are unique to *M. leprae* and no homologues in *M. tuberculosis* need to be looked into.[31–33]
4. *PCR and more specifically RT PCR* for detection on *M. leprae* encoding specific genes or repeat sequences is potentially highly sensitive and specific since it detects *M. leprae* DNA in 95% of multibacillary and 55% of paucibacillary patients. Other DNA techniques – Transmission by VNTR analysis with the study of more loci, recognised as being variable in leprosy patients. SNPs as diagnostic tools need greater study.[34–37]
5. *Other tests* – further research into various chemokines and cytokines for the diagnosis of leprosy and reactions.[38,39]
6. Further research into *Non Invasive Tests* such as High resolution sonography, MRI and Nuclear magnetic resonance. They have shown that arterial and venous flow is altered in damaged nerves and in active ENL and are more patient friendly.[40–42]
7. *Newer Culture Methods* – as the older methods of mouse foot pad culture remain time consuming, labour intensive and expensive.[43–45]
8. Even though most of the above diagnostic tests remain more expensive and out of reach of most people, they should be fine tuned for use in difficult cases.

C) Chemotherapy

1. Further research into newer antimicrobial agents with various degrees of bactericidal activity against *M. leprae* is needed. See Table 1.[46–54]

Table 1. Newer drugs displaying bactericidal activity against *M. leprae*

Drug	Class	Bactericidal activity in mice*	Bactericidal activity in human*	Unit cost
Pefloxacin	Fluroquinolone	++	++	Moderate
Ofloxacin		++	++	Moderate
Moxifloxacin		+++	+++	High
Clarithromycin	Macrolide	++	++	Moderate
Minocycline	Tetracycline	++	++	Moderate
Rifapentine	Rifamycin	+++	Not done	High
R207910	Diarylquinoline	+++	Not done	Not commercially available
Linezolid	Oxazolidinone	+	Not done	High

* Based on the activity of (+) for dapsone and (+++) for rifampicin.

2. Research into costs and cost-benefit scenarios.
3. Research into further simplification of treatment for better adherence and monitoring, for e.g. the following combination was suggested: RFP 900 mg (or, RIF 600 mg)–MXF 400 mg–CLR 1000 mg (or, MIN 200 mg), all drugs administered once-monthly under supervision(the dosages are for adults).[52]
4. For the regimen targeting patients with RIF-resistant leprosy – urgent research is needed. One proposed regimen was an initial 6-month intensive phase, followed by an additional 18-month continuation phase.[52]
   - Intensive phase: MXF 400 mg–CLO 50 mg–CLR 500 mg–MIN 100 mg, daily for 6 months;
   - Continuation phase: MXF 400 mg–CLR 1000 mg–MIN 200 mg, once monthly for an additional 18 months.
5. If preliminary clinical trials demonstrate that the simplified regimen (i.e. the regimen for patients with RIF-susceptible MB leprosy and is administered once-monthly for 12 months) is reasonably well-tolerated, and provide early evidence of effectiveness for treating MB leprosy, then the second step of clinical trials, i.e. controlled clinical study, should be undertaken.
6. In the controlled clinical study, multiple regimens, including the current MB regimen as positive control should be compared. Each arm of the trial requires at least several hundreds of MB patients, and follow-up of at least 7 years after completion of treatment.
7. Better methodologies are required for accelerate the development of new MDT regimens as the mouse footpad system is technically demanding, time consuming and development of tests for measuring bactericidal activity against *M. leprae* more rapidly and precisely would be helpful.
8. A simple and reliable surrogate marker for measuring the sterilising activity against *M. leprae* – the most appropriate indicator of the ability to shorten the duration of treatment.

Chemoprophylaxis: Chemoprophylaxis is feasible only in a strong leprosy control programme.[55–57]

1. Research into more effective regimens is needed for very high risk groups. These groups need to be correctly identified first.

2. Tools to detect sub-clinical leprosy to study tailor-made prophylactic treatment regimens are required.
3. Further operational/health systems research to identify characteristics of the public health system that are critical for a successful implementation of chemoprophylaxis under routine leprosy control programme conditions.
4. Regimens of prophylaxis also remains an unexplored area.

D) Prevention of Disability

1. Operational research on making self-care more successful.
2. Research on the role of stigma and self-stigma in de-motivating people, and conversely on the importance of individual empowerment in giving people a positive motivation, needs to be developed further.
3. Research on the best ways of ensuring adequate access to appropriate footwear, on a country-by-country basis.
4. Reactions and neuritis – Further research into methods of integrating knowledge on reactions and neuritis into the general health services, where the majority of people with leprosy are now treated. Therefore, simplified methods of monitoring, or even self-monitoring by patients themselves, need to be developed and tested, along with straightforward guidelines for referral and management.
5. Neuropathology – there are three major areas for further research-mechanisms of neuropathy in leprosy, diagnosing neuropathy – screening and diagnostic tests and treatment of neuropathy. There is also a need to study early damage in a research setting, so early diagnosis with more sophisticated, but also more sensitive, tests must also be studied.
6. Further research on optimal dose and duration of steroid treatment. Other immunosuppressant drugs have only been minimally examined so far, need to be studied further.
7. Identification of best practice in the treatment of neuropathic pain in leprosy and the role of nerve decompression surgery.
8. Research into more effective methods of rehabilitation to enable affected persons to be more independent and to increase their social interaction. Stigma reduction is essential and is an important social concern.
9. Multi-centric, multi-disciplinary research on operational issues of 'prevention of disability' with comparison between leprosy institutions and the general health systems.

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Annexe I: Methodology of the Workshop

Each of the topics under consideration was accorded approximately $1\frac{1}{2}$ to 2 hours. For each topic there was a lead speaker and chief discussants.

The lead speaker presented a detailed summary on each topic with references for about 30 to 45 minutes. This report had been previously circulated to all workshop members. The chief discussant articulated for 20 to 30 minutes, after which the matter was open for discussion by the house.

The morning session on the first day dealt with epidemiology and chemotherapy, and in the afternoon session, the topics of diagnosis/classification and prevention of disability were considered.

The second day was devoted to discussion of unfinished topics and preparation of a draft of the workshop.

Annexe II: Participants of the Pre Congress Workshop No. 7

S. No.	Category	Name	Speaker	Area
1	Convener	Dr P. S. S. S. Rao		India
2	Epidemiology	Dr Jan Hendrik Richardus	Chief discussant	Netherlands
3		Dr Masanori Kai	Speaker	Japan
4		Dr H. Joseph Kawuma	Chief discussant	Africa
5		Dr Paul Fine	Lead speaker	UK
6		Selvasekar Abraham		India
7		Dr Maria Leide de Oliveira		Brazil
8	Diagnosis and Classification	Dr Vaneja Shetty	Lead speaker	India
9		Dr Indira Nath	Chief discussant	India
10		Dr Kiran Katoch	Chief discussant	India
11		Dr Murdo MacDonald		Nepal
12	Chemotherapy	Dr Baohong Ji	Lead speaker	France
13		Dr Linda Oskam	Chief discussant	Netherlands
14		Dr W. C. S. Smith	Chief discussant	UK
15	Prevention of Disability	Dr Paul Saunderson	Lead speaker	USA
16		Dr R. K. Mutatkar	Chief discussant	India
17		Dr Wim Brandsma		Ethiopia
18	General	Dr Mohit Mehndiratta		India
19		Dr P. Krishnamoorthy		India
20		Dr Ana Claudia		Brazil
21		Dr Jannine Ebenzo		Africa
22		Dr Ruchika Chandna		India
23		Dr P. K. Dass		Amsterdam
24		Dr Casabianca		India
25		Dr A. Antony Samy		India