Report on Leprosy

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1. Executive summary

In 1977, the World Health Organization (WHO) Expert Committee on Leprosy estimated the global number of leprosy cases to be over 12 million. In 1981, WHO convened the Study Group on Chemotherapy for Leprosy Control, which recommended combined-drug regimens based on supervised intermittent administration of rifampicin for both multibacillary (MB) and paucibacillary (PB) leprosy. Thanks to the implementation of this multidrug therapy (MDT), substantial progress in leprosy control has been achieved and over 12 million cases had been cured by 2002. However, to date there is no clear evidence of an impact of introduction of MDT on the rate of detection of new cases. Approaches to address this question are impeded by a lack of fundamental knowledge about the epidemiology of leprosy, the sources of infection, its precise mode of transmission and the importance of contact patterns.

Worldwide, and in spite of the dramatic impact of MDT on leprosy prevalence, 2-3 million people are still living with deformities due to leprosy. As new cases remain at risk of developing nerve impairment, detecting, managing and understanding the mechanism(s) involved in nerve damage remain a high priority for research programmes. Studies to date have not provided the optimal approaches needed to assure the prevention and management of nerve impairment.

In most leprosy endemic countries, leprosy control activities have been integrated into the general health services or are in the process of being integrated. Research priorities should be directed at assessing and improving the quality of leprosy services in integrated settings, addressing in particular issues of access, case detection, compliance, prevention of disability, and referral services.

Multidisciplinary approaches that enhance research are essential to each research theme, including social sciences approaches, which have been somewhat neglected recently as scientists have focused more on the causative agent of leprosy. Collaboration with researchers in other topics should be actively encouraged. For example, nerve damage studies should be linked with research in the neurosciences, while engagement of tuberculosis researchers is of particular relevance in areas such as new drug exploration and vaccine and diagnostics development. TDR has a specific role to play in sustaining the momentum in leprosy research through capacity strengthening, promoting coordination of research proposals, and facilitating funding opportunities for the identified research priorities.

The Scientific Working Group produced a clear consensus on the major possibilities for leprosy research based on the expressed research needs from endemic countries and the current
research opportunities. The next step will be to develop these major research priorities into detailed programmes and research protocols. Specific proposal development workshops will be convened in 2003 to develop the proposals and protocols for research programmes in the identified areas: transmission/diagnostics, nerve damage, and integration into the general health services.
2. Background

The World Health Organization (WHO) leprosy programme was responsible for the global implementation of multidrug therapy (MDT) and for setting an elimination target, originally for the year 2000. More recently, WHO formed a Global Alliance for the Elimination of Leprosy (GAEL) with the aim of reaching the elimination target (less than 1 case per 10 000) in all countries by 2005. A number of organizations have emphasized the need to sustain control activities after 2005, and to care for patients who are permanently disabled. A limited operational research component is included under the GAEL.

A number of other events preceded the convening of the Scientific Working Group (SWG) on leprosy in 2002. These included the recent WHO Technical Advisory Group (TAG) held in Brasilia, which reiterated its previous recommendations that the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) should maintain/focus its research efforts and address the research needs of leprosy control, including:

- development of strategies to ensure sustainability of control activities after the year 2005;
- development of partnerships necessary for maintaining a coordinated and effective research programme;
- regeneration of dwindling research capacity in the leprosy disease endemic countries (DECs).

Another event was the TDR strategic review in 1999/2000, which concluded that TDR should expand its analytical capacity, contribute more to global agenda setting, strengthen links with control, and engage more in implementation research to ensure that new tools or systems are rapidly adopted by control programmes.

The SWG was expected to take into account the results and recommendations for further research as presented recently in the Report of the International Leprosy Association (ILA) Technical Forum (International Journal of Leprosy and Other Mycobacterial Diseases, 2002, 70 [1 Suppl]:S1-62), and to take into consideration new research findings presented at the International Leprosy Congress held in Salvador, Brazil, August 2002.
3. Rationale for the Scientific Working Group

Current control measures have greatly reduced the prevalence of leprosy and are probably reducing its transmission, although new case detection rates have remained relatively stable, with only a slight downward trend, until recently. New control measures such as leprosy elimination campaigns have been implemented, but their impact remains uncertain. There is a clear need for additional innovative ways of increasing/facilitating case detection, for better understanding of leprosy transmission, and for better appreciating how to transfer leprosy control activities into the general health services.

The global leprosy research effort has dwindled and many scientists have moved to TB research. New discoveries, especially the sequencing of the *Mycobacterium leprae*, *M. tuberculosis* and other mycobacterial genomes, have opened up new opportunities for leprosy research which remain to be fully exploited. Importantly, there is little research focus in support of the burning operational needs for ensuring sustainable leprosy control beyond 2005.
4. Goals, objectives and expected outcomes

The GOALS OF THE SWG were:
• to recommend a leprosy research agenda and demonstrate a clear rationale for TDR to continue leprosy research, at least until the next SWG meeting in 2006/2007;
• to develop a rational, focused strategy for conducting leprosy research directly relevant to control needs, in partnership with the WHO leprosy unit, GAEL, and various research partners;
• to assess what new scientific opportunities exist to develop needed tools.

The OBJECTIVES OF THE SWG were:
• to summarize the current status of leprosy control;
• to define the current/future research needs, including with regard to deficiencies in knowledge and the effectiveness of currently available tools and strategies;
• to review leprosy research activities globally and identify scientific opportunities;
• to identify the gaps between needs and ongoing research efforts;
• to agree upon means of addressing the gaps, including strengthening existing and building new partnerships.

EXPECTED OUTCOMES
The SWG was expected to provide TDR with an overall strategy and scientific direction for leprosy research over the next five years, together with an agreed list of expected outcomes and potential impact(s) of this research programme.
5. Partners

The WHO leprosy unit and partners in GAEL, including leprosy control programme managers in the six high burden countries, were considered essential partners for a successful SWG meeting. WHO inputs into the assessment of leprosy burden and leprosy vaccine/diagnostics research were also to be included, and major global research institutions involved, including the Indian Council of Medical Research, Oswaldo Cruz Foundation (FIOCRUZ), University of Colorado, Institut Pasteur, Aberdeen University, Royal Tropical Institute, Erasmus University, London School of Hygiene and Tropical Medicine, and various leprosy nongovernmental organizations (NGOs).
6. Meeting report

MAJOR CHALLENGES AND PRIORITY RESEARCH NEEDS

MDT has reduced the global prevalence of leprosy enormously and cured millions of patients, and in some countries case detection rates have shown a progressive decline. However, review of available data on trends in case detection rates shows no evidence of an impact associated with the introduction of MDT, and these rates remain high in some countries. The extent to which the figures provide a measure of leprosy transmission is unclear since case detection rates are influenced by multiple and complex operational factors, including the inadequacies of diagnosing patients based on presence of skin lesions. Present field diagnostic methods sometimes lead to substantial over-diagnosis of a portion of paucibacillary patients; they also lead to under-diagnosis, especially of early multibacillary patients. Misdiagnosis and underdiagnosis of leprosy is likely to increase in decentralized and integrated leprosy control services, where staff involved in diagnosis of leprosy are less experienced.

Simulation models based on case detection data suggest that, under current circumstances, there is little likelihood of any dramatic downturn in the number of new cases over the next decade. Lessons from other diseases suggest there is a real danger that failure to meet expectations of reduced patient numbers will have a significant negative impact on future prospects for leprosy control and its integration into the general health services. The problems are compounded by lack of fundamental knowledge about the epidemiology of leprosy, the sources of infection, the precise mode of transmission, and the importance of contact patterns. To approach the goal of eradication of leprosy, and perhaps even sustain current successes, a new need is to identify new intervention strategies that target reduction of transmission. Given the difficulties of measuring transmission based solely on new case detection rates, there is a need for objective measures that better reflect transmission.

Other major research challenges and needs include:
• Understanding the contribution of operational factors to delayed diagnosis and initiation of treatment, and of contagiousness prior to development of symptoms.
• Developing more specific diagnostic tools for field application.
• Investigating novel intervention strategies such as chemoprophylaxis and immunoprophylaxis in terms of ability to interrupt transmission, cost effectiveness, and compatibility with health systems and local cultural considerations, particularly focusing on defined high risk groups or areas.
• Using epidemiological and community based approaches to identify high risk groups from an operational and intervention perspective.
• Developing tests to accurately identify persons who are in contact with leprosy and have become infected, in order to understand transmission. Several tests, based on combined measurement of humoral and cellular immune responses and in some instances on direct evidence of presence of bacteria or their products, are under development. These tests need to be evaluated in the context of carefully defined epidemiological questions.
• Developing approaches to distinguish different strains of M. leprae in order to help understand its transmission patterns. In an analogous way, methods used to distinguish different strains of mycobacteria were very important in understanding the transmission patterns of tuberculosis.
• Exploitation of existing data and generation of improved data sets in order to enhance the use of mathematical models to gain better insight into the dynamics of leprosy infection, predict
the effect of different interventions, and provide an important advocacy tool.

Nerve function impairment and reactions represent major challenges and priorities, both for prevention of infection and development of effective treatments. Nerve function impairment, which limits a person’s activities and affects his/her participation in society, is a result of infection with *M. leprae* and the host’s response to this infection; it can be acutely associated with reactional episodes, either before diagnosis of leprosy or during MDT treatment. The proportion of new cases with evidence of nerve function impairment at diagnosis varies considerably between countries and in many situations is greater than 20% of all new cases. The risk of reactions during MDT treatment is low in paucibacillary (PB) patients but can be as high as 50-60% in multibacillary (MB) patients with pre-existing nerve damage. Impairment of sensory, motor and autonomic nerve function leads to a progressive process of recurrent trauma, tissue damage and tissue loss affecting the eyes, hands and feet. The consequences of leprosy have a profound impact on individual patients, their families and communities and are associated with much of the stigma associated with the disease.

**Nerve function impairment and reactions represent major challenges and priorities – both for prevention and development of effective treatments.**

**ONGOING GLOBAL RESEARCH EFFORTS**

Research on the epidemiology of leprosy is limited by the problems associated with a low incidence of disease, a long incubation time, and a lack of relevant tools. Some studies to evaluate the effect of chemoprophylaxis are under way, e.g. in Bangladesh, India and Indonesia, while in Cuba, treatment of serologically-positive contacts is routine practice. Immunoprophylaxis studies in South India and Malawi are being followed up, and the effect of repeat BCG vaccination is being assessed in Brazilian schoolchildren.

Serological tests for antibodies to *M. leprae* phenolic glycolipid –1 (PGL-1) have been extensively characterized in endemic settings, and rapid simple assays are now being evaluated in the field. Attempts are under way to identify antigens suitable for use as improved skin test reagents; these are undergoing initial evaluation in Nepal and Brazil. Recombinant proteins and synthetic peptides are also being investigated as potentially specific antigens for use in blood-based tests to measure T cell responses to *M. leprae* as an indicator of infection.

Efforts are under way in a few laboratories to identify genetic polymorphisms as the basis for development of strain typing systems for *M. leprae*. Variations in short tandem repeat loci appear particularly promising.

A range of research efforts addressing nerve damage are currently being undertaken. Although largely uncoordinated in the past, recent developments have led to more coordination of these efforts. Work in progress includes, in the basic sciences, study of the mechanisms of neurotropism and the pathogenesis of nerve damage, while a number of epidemiological studies have provided important understanding of the risk factors for nerve function impairment and reactions. Several clinical trials of interventions for prevention and treatment of reactions are nearing completion in India, Bangladesh and Nepal, based on new regimens and new drugs, while a major research initiative, INFIR, is in progress using a multidisciplinary approach to address the pathogenesis of nerve damage and reactions, novel treatments, recurrent reactions and delay in diagnosis.
RESEARCH OPPORTUNITIES

The availability of *M. leprae* and other mycobacterial genome sequences provides important opportunities for identifying novel *M. leprae*-specific antigens that can be used to develop improved tests for infection. This sequence information is also central to prospects for developing molecular epidemiology approaches for leprosy. In addition, leprosy research is well placed to benefit from the rapid advances in post-genome technologies such as microarrays and bioinformatics.

Research on transmission is particularly timely given the current epidemiological situation in which MDT is reducing the prevalence of leprosy but leaving a sustained level of new cases.

A specific research opportunity to explore neurotropism in leprosy is provided by the genome project, while opportunities to investigate the basic mechanism(s) of nerve damage in leprosy are provided by new Schwann cell models of *M. leprae* infection. A new generation of immunoregulatory drugs and TNF-α inhibitors is providing new therapeutic opportunities, while the development of standardized outcome measures from the recent clinical trials for nerve function and reactions, and measurements of activities and participation, are providing opportunities for new clinical studies.

The TDR Scientific Working Group on Leprosy identified four specific research priorities – transmission, diagnostics, nerve damage and reactions, and the integration of leprosy control activities. A number of issues are relevant to each of these research priorities.

**Transmission/diagnostics**

To sustain current successes and to approach the goal of eradication of leprosy, there is a need to identify new intervention strategies that complement MDT by targeting reduction of transmission.

**Research priorities**

1. Evaluation of the impact on leprosy transmission of chemoprophylaxis and immunoprophylaxis with vaccines of proven efficacy (BCG and ICRC [an Indian version of BCG]). Controlled trials should include evaluation of relevant objective tests for infection in addition to standardized case detection. Data from ongoing trials and programmes should be used to strengthen expertise in modelling approaches to understand leprosy transmission and for scenario analysis.

2a. Evaluation of use of PGL-1 serology as a marker for high risk groups suitable for chemoprophylaxis or other interventions.

2b. Assessment of the utility of skin test reagents based on fractionated *M. leprae* or recombinant proteins as an epidemiological tool to identify infected individuals. Comparison of recombinant *M. leprae*-specific proteins and synthetic peptides with blood-based tests involving measurement of T cell responses, e.g. gamma interferon production, with respect to sensitivity, specificity and operational feasibility.

2c. Further improvement of the usefulness of polymerase chain reaction (PCR) detection of *M. leprae*, and development and validation of strain-typing systems for *M. leprae*. This should include generation of genome sequence data from additional *M. leprae* isolates, coordination between different research groups working globally, and testing of assays in well-defined epidemiological settings.

3. Detailed epidemiological studies and analyses of the contributions of different exposure patterns to the development of disease and positivity in tests for infection.
Funding strategies
TDR is well placed to coordinate a proposal for a major multidisciplinary project on leprosy transmission which would be appropriate for external funding. Such a proposal would require initial funding of collaborative workshops to bring together partners from different countries and disciplines for formulating trial designs and standardizing relevant assays and reagents.

TDR comparative advantage
Studies of leprosy transmission should be carried out in different geographic settings and should involve a range of expertise from bench scientists and clinicians to epidemiologists, programme managers, economists and social scientists. TDR is uniquely placed to bridge interactions between partners in developed and developing countries and to bring together the appropriate spectrum of expertise.

The development and application of tests for infection provide opportunities for scientific collaborations and research strengthening in the key disciplines of molecular biology, bioinformatics, immunology and epidemiology. TDR is the ideal coordinator for such activities.

Findings from the proposed research programme will have obvious and immediate implications for implementation and control policies. Standing at the interface of research and control, TDR is well-placed to facilitate such progress.

TDR has a key role to play in sustaining momentum in leprosy research by encouraging the interests of basic scientists and motivating control personnel. Research on leprosy transmission addresses both of these aspects.

Nerve damage
Although MDT has had a dramatic impact on prevalence of leprosy, still 2 to 3 million people worldwide have deformities due to the disease. In addition, in many parts of the world there has been little impact on the rate of detection of new cases, and these new cases remain at risk of developing nerve impairment. Thus detecting, managing and understanding the mechanisms involved in nerve damage remain a high priority. Trials of prophylaxis and treatment of nerve damage have not provided optimal approaches for the prevention and management of nerve impairment. Therefore a combination of clinical and epidemiological research and mechanistic studies is required for the identification of risk factors, management, and prevention of nerve damage. We recommend the following areas as priorities for research.

Research priorities
1. Investigation of the role of prophylaxis with steroids in preventing nerve damage.
2. Development of methods to identify patients at high risk of going into reaction.
3. Research on the management of patients at high risk.
4. Research on new treatments for nerve damage, including new steroid regimens, new immunosuppressive drugs, and specific inhibitors of cytokine or signalling pathways.
5. Immunopathological and/or cell culture approaches to understanding the interaction between M. leprae and host cells (Schwann cells, macrophages, dendritic cells) at the molecular level. Such studies might lead to the development of:
   - Improved understanding of the mechanism of action of steroids;
   - New markers of nerve damage;
   - New tools for the prevention of nerve damage;
   - Improved treatments for nerve damage and nerve regeneration.
Funding strategy
This topic is appropriate for seed funding by TDR and of potential interest to several NGOs.

Research to improve integration
In most leprosy endemic countries, leprosy control activities have been integrated into the general health services or are in the process of being integrated.

Major advantages of this integration are increased accessibility of diagnosis and treatment, decreased stigma, and increased sustainability and cost-effectiveness. However, there is concern that development of integrated services will lead to deterioration in quality of care for leprosy patients. Regimens that shorten the duration of treatment and are uniform for all patients will considerably simplify administration of treatment through the general health services.

Research priorities
1. Assessment and improvement of quality of leprosy services in integrated settings, addressing, in particular, issues of access, case detection, compliance, prevention of disability, and referral services.
2. Assessment of new drug regimens for use in integrated settings. The proposed multicentre study on a six-month uniform MDT regimen for all leprosy patients addresses the need for a simplified treatment scheme.
3. Assessment of the current situation with regard to rifampicin resistance.

Funding strategy
Co-funding for the above three research areas should be sought through various NGOs and multilateral funding agencies.

Cross-cutting issues
The TDR Scientific Working Group on Leprosy identified four specific research priorities – transmission, diagnostics, nerve damage and reactions, and the integration of leprosy control activities. A number of issues are relevant to each of these priorities, for which important research opportunities, underpinned by post-genomics research, were provide Gd by sequencing of the M. leprae genome. Multidisciplinary approaches that enhance research are essential to each of the research themes, including social sciences approaches, which have been somewhat neglected recently as scientists have focused more on the causative agent of the disease. Collaboration with researchers in related topics should be actively encouraged. For example, nerve damage studies should be linked with research in the neurosciences, while collaboration with tuberculosis researchers is of particular relevance in areas such as new drug exploration and vaccine and diagnostics development. It is recognized that HIV may have a potential impact on each area of research. TDR has a specific role to play in sustaining the momentum in leprosy research through capacity strengthening, promoting coordination of research proposals, and facilitating funding opportunities for each of the identified research priorities.
7. Next steps

The Scientific Working Group achieved a very clear consensus on the major possibilities for leprosy research based on the expressed research needs from endemic countries and the current research opportunities. The next step is to develop these major research priorities into detailed programmes and research protocols. Specific workshops will be convened in 2003 to develop the proposals and protocols for research programmes in the four areas: transmission, diagnostics, nerve damage, integration. Draft research protocols will be prepared by mid-2003 and finalized for submission to funding agencies by the end of 2003.

Time frame:

- November 2002 . . . SWG
- January 2003 . . . SWG report
- Mid-2003 . . . Workshops and draft proposals
- End-2003 . . . Proposals submitted to funding agencies