A Research Strategy to Develop New Tools to Prevent Leprosy, Improve Patient Care and Reduce the Consequences of Leprosy

Five Year Leprosy Research Strategy

Approved by ILEP Board October 2011

Coordinator: Prof. WCS Smith

Summary: A Research Strategy to Develop New Tools to Prevent Leprosy, Improve Patient Care and Reduce the consequences of Leprosy

The Importance
The Global Leprosy Programme has had a dramatic impact on the prevalence of registered cases of leprosy over the last 20 years through the implementation of short course multi-drug therapy (MDT) treatment. However, further advances in the field of leprosy are hindered by the lack of new tools to address the challenge of apparent persistence in transmission and incidence, and the long-term consequences of the disease.

The Strategy
This strategy was developed by the Technical Commission of ILEP to provide a framework to prioritise research, to identify the steps needed to develop and implement new tools, and to identify funding gaps. The strategy focuses on applied research, either *technology transfer* or research to *evaluate effectiveness* of interventions where there is already proof of principle. More basic research and proof of principle are important but are outside the scope of this five year strategy.

The Principles
The strategy is composed of eight themes, but research in these themes should be fully integrated mainly through the use of common field sites. The integration of research with other Neglected Tropical Diseases and diseases of poverty, and multi-disciplinary approaches are strongly advocated. Millennium Development Goal (MDG) 6 targets the reduction in the burden of disease but tackling poverty (MDG1), education (MDG2), gender equality (MDG3), child health (MDG4), maternal health (MDG5) and partnerships (MDG8) are all important for leprosy.

The Logistics
This strategy is based on the achievement of deliverables within five years at an estimated cost of £24 million. A number of the projects are already in progress, some are developed and requiring funding, while other areas are gaps representing urgent priorities. The key components are presented in the table:

Research Themes	Technology Transfer	Evaluate Effectiveness
1. Prevention	Roll out chemoprophylaxis	Chemoprophylaxis + BCG Assess new TB vaccines
2. Early Detection	Prevent delayed detection	Test neuro, immune and molecular diagnostics
3. Chemotherapy	Improve adherence	U-MDT and new regimens
4. NFI and Reactions	Use of monofilaments	Early detection, optimal steroids, ENL treatment
5. Prevention of Disability	National programmes, integration with 'Legs to stand on'	Novel treatments for plantar ulcers
6. Community Based Rehab.	Increase CBR participation	Test CBR guidelines
7. Stigma Reduction and Advocacy	Implementation of proven interventions Translate UN Guidelines	Test interventions to reduce stigma Test Patients Charter
8. Health/Social Care Integration	Integration with Primary Care, CBR and NTDs – in low endemic settings	

RED – funding required GREEN – funded and in progress

A Research Strategy to Develop New Tools to Prevent Leprosy, Improve Patient Care and Reduce the Consequences of Leprosy

The Importance

The Global Leprosy Programme has had a dramatic impact on the prevalence of registered cases of leprosy over the last 20 years through the implementation of short course MDT treatment. However, further advances in the field of leprosy are hindered by the lack of new tools to address the problems of continuing new case detection and the long-term consequences of the disease. The challenge is to develop a five year research programme to tackle the big issues in leprosy that will have an impact on transmission and lead to reduction in new cases of leprosy, earlier diagnosis of leprosy before disabilities develop, better adherence with chemotherapy, chemotherapy that is more acceptable, has less side effects and reduces the risk of drug resistance, better diagnosis and treatment of reactions to minimise disability, increased coverage of prevention of disability to minimise impairments, better access to rehabilitation and interventions to reduce stigma and discrimination against those affected by leprosy.

The development of new strategies to address the challenge of leprosy and to respond to emerging threats to the Global Leprosy Programme is hindered by the lack of research (3). The current global strategy is based on technologies that are more than 25 years old. There is an urgent need for research to develop innovations that could lead to the eradication of leprosy.

The Strategy

Our co-ordinated approaches to leprosy research in the last decade have worked well and been fruitful – for example INFIR[1], IDEAL[2], and drug-resistance surveillance. However, these collaborations have been largely limited by funding constraints, and have focused on one topic. The aim of this Research Strategy is to pull together the whole programme of research based on multi-disciplinary working so that we can share methods, research sites and avoid duplication. It needs to be based on strong North-South partnerships and provide new evidence of effective interventions that can be implemented across all regions and contexts. It is also important that leprosy research becomes more integrated with research in other Neglected Tropical Diseases. This is important as a requirement of many funding streams, but there are other advantages in terms of knowledge exchange, access to technology, and synergies in the conduct of field research. Millennium Development Goal (MDG) 6 targets the reduction in the burden of disease but tackling poverty (MDG1), education (MDG2), gender equality (MDG3), child health (MDG4), maternal health (MDG5) and partnerships (MDG8) and all important for leprosy.

The Principles

The strategy is composed of eight themes, but research in these themes should be fully integrated through the use of common field sites, shared methods and co-ordinated by a Steering Group. The integration of research with other Neglected Tropical Diseases and diseases of poverty, and multi-disciplinary approaches is

[1] The ILEP Nerve Function Impairment in Reaction
[2] Initiative for Diagnostic and Epidemiological Assays for Leprosy

strongly advocated. The Strategy should include strengthening the research capacity in South institutions.

The leprosy research themes are as follows:

1. Prevention of leprosy
2. Early detection
3. Chemotherapy
4. Nerve function impairment and reactions
5. Prevention of disability
6. Community-Based Rehabilitation
7. Stigma reduction and advocacy
8. Health and social care integration

The Logistics

This strategy is based on the achievement of deliverables within five years. A number of the projects are already in progress, some are developed and requiring funding, while other areas are gaps representing urgent priorities. The deliverables have been defined as *technology transfer* where the evidence of effectiveness exists, but roll out to scale is required including work on feasibility, acceptability and cost-effectiveness; and deliverables where *evaluation of the effectiveness* of interventions is needed. Research which is further upstream including early drug development, vaccine development and more basic research where patient benefit is unlikely to be achieved within five years are clearly important, but are outside the scope of this research strategy.

The case for each part of the strategy is presented in a standard way in the appendix by describing the problem, its importance, the objective of the work programme, the activities, relationship to other NTDs or MDGs, timescale, the deliverable, potential key investigators, the status of the research including work ongoing and estimated costs.

The Process

The initial work on the Strategy has been based on reviewing current recommendations (1, 2) for research in leprosy and the most recent review of research evidence (3). This current version of the Strategy has been edited following a period of consultation, taking account of comments and criticisms from individuals and ILEP Member associations. The Strategy was presented and discussed at the ITC and ILEP Multilateral/Cooperation Meetings in London in October, 2011 and subsequently approved by the ILEP Board on 14th October, 2011.

References

1. World Health Organization. 8th Expert Committee on Leprosy, World Health Organization, Geneva, 2011.

2. World Health Organization. Enhanced Global Strategy for Further Reducing the Disease Burden due to leprosy (2011 – 2015). World Health Organization, South-East Asia, 2009.

3. ILEP Technical Commission. Review of leprosy research evidence (2002-2009) and implications for current policy and practice. Leprosy Review 2010;81: 228-275.

Appendix : Research Theme Cases

1. Prevention

Roll out of chemoprophylaxis	**Technology transfer**
Problem	Single dose rifampicin reduces new cases in close contacts by more than 50% but it is not routinely implemented
Importance	30% of new cases are in close contacts so implementation could reduce new cases
Objective	Develop methods to achieve 80% coverage of chemoprophylaxis in close contacts
Activities	Field studies of acceptability, logistics, cost-effectiveness of chemoprophylaxis
Relationship to NTDs/MDGs	Chemoprophylaxis is a strategy used in a number of other NTDs
Timescale	3 years
Deliverable	Enhanced contact surveillance and methods to reduce new cases in contacts through roll out chemoprophylaxis
Key investigators	WHO, ILEP – Richardus, Smith, Saunderson
Status	Not funded
Estimated costs	£500,000

Test chemoprophylaxis + BCG	**Evaluate effectiveness**
Problem	Chemoprophylaxis only effective in first 2 years
Importance	Chemoprophylaxis + BCG could provide greater and longer protection for close contacts
Objective	Evaluate the effectiveness of chemoprophylaxis +BCG
Activities	Clinical trial
Relationship to NTDs/MDGs	Both methods used in other NTDs
Timescale	5 years
Deliverable	Evidence to enhance and sustain reduction in new cases in contacts
Key investigators	Richardus
Status	Funded (Maltalep) – in progress
Estimated costs	£ 250,000

Test new TB vaccines	**Evaluate effectiveness**
Problem	New TB vaccines to replace BCG are under trial
Importance	Need to ensure the TB vaccine are effective against leprosy too
Objective	Evaluate the effectiveness of TB vaccines against leprosy
Activities	Add on to existing studies
Relationship to NTDs/MDGs	Relevant to TB
Timescale	5 years
Deliverable	New vaccines effective against leprosy
Key investigators	IDRI/ALM
Status	Under consideration with ALM/IDRI
Estimated costs	£ 500,000

2. Early detection

Prevent delay in diagnosis	Technology transfer
Problem	A proportion of patients have visible disability at the time of diagnosis
Importance	The presence of irreversible disability at the time of diagnosis has long term consequences
Objective	Use existing methods to identify barriers to delayed diagnosis and implement solutions in different settings
Activities	Interviews with patients with disability at diagnosis to identify patient and health system problems and develop solutions
Relationship to NTDs/MDGs	Delayed diagnosis is a common issues for all NTDs
Timescale	3 years
Deliverable	Rapid methods to reduce disability in new cases by identifying and solving problems of delayed diagnosis
Key investigators	WHO, ILEP, Smith, Nicholls
Status	Not funded
Estimated costs	£500,000

Test neurological, immunological and molecular diagnostics	Evaluate effectiveness
Problem	Early diagnosis is currently based on clinical examination – there are no reliable diagnostic tests for early leprosy
Importance	Early diagnosis and treatment will prevent the occurrence of disability due to leprosy – potential link to chemoprophylaxis
Objective	Develop acceptable, feasible and valid diagnostic tests
Activities	Field studies to evaluate novel neurological, immunological and molecular methods of early diagnosis and measures of exposure
Relationship to NTDs/MDGs	Early diagnostic methods could be applied for other NTDs – relation to tuberculosis and Buruli ulcer
Timescale	5 years
Deliverable	New, rapid, diagnostic test and test of exposure to M.leprae for early detection and targeting prophylaxis
Key investigators	IDEAL and INFIR groups Potential collaboration with TDR and FIND, Geneva
Status	Part funded
Estimated costs	£3,000,000

3. Improved Chemotherapy

Improve adherence with MDT	**Technology transfer**
Problem	The information on compliance with MDT is based on distribution of MDT rather than completion of treatment – reports suggest that adherence is much lower
Importance	A high level of adherence to MDT is required to achieve a low relapse rate and prevent emergence of drug resistance
Objective	Assess adherence and apply evidence from other treatment programmes to improve treatment completion rates
Activities	Patient interviews, random inspection and urine testing to asses adherence followed by interventions to improve adherence
Relationship to NTDs/MDGs	Common problem in NTD treatments
Timescale	3 years
Deliverable	Reduced risk of relapse and drug resistance by improved adherence with MDT
Key investigators	WHO, ILEP
Status	Not funded
Estimated costs	£500 000

U-MDT Trial	**Evaluate effectiveness**
Problem	The current MDT regimen requires classification of patients and 4 different regimens to be distributed
Importance	Classification is error prone and 4 regimens leads to both non-availability and drug wastage
Objective	Test the effectiveness of a single regimen for all patients
Activities	Trial
Relationship to NTDs/MDGs	Specific to leprosy
Timescale	5 years
Deliverable	Simplified, single regimen for all patients
Key investigators	TDR, WHO
Status	On going in India and China
Estimated costs	TDR funded

New MDT Regimens	**Evaluate effectiveness**
Problem	Adverse effects of current MDT, dapsone resistance is common, threat of rifampicin resistance
Importance	Need proven, alternative regimens
Objective	Develop new combinations of existing drugs (TB)
Activities	RCT of new combinations of existing drugs
Relationship to NTDs/MDGs	Common issues with tuberculosis
Timescale	5 – 10 years
Deliverable	Effective alternative to MDT to combat resistance
Key investigators	WHO, TDR
Status	Not funded
Estimated costs	£5,000,000

4. Prevention and treatment of reactions and NFI

Use of monofilaments	**Technology transfer**
Problem	New nerve function impairment is detected too late to effectively treat
Importance	Irreversible nerve function impairment leads to life-long, progressive disability
Objective	Test effectiveness of providing all patients and field staff with monofilaments with education
Activities	Series of pilot studies and roll out to scale
Relationship to NTDs/MDGs	Shared technology with foot care in diabetes
Timescale	3 years
Deliverable	Reduce disability by improved early diagnosis of nerve impairment
Key investigators	ILEP
Status	Non funded
Estimated costs	£250,000

Early detection of NFI/reactions	**Evaluate effectiveness**
Problem	Nerve function impairment is detected late and optimal steroid treatment is uncertain
Importance	Irreversible nerve function impairment leads to life-long, progressive disability
Objective	Test new early nerve impairment detection, different steroid regimens and 2nd line treatments
Activities	Clinical trials
Relationship to NTDs/MDGs	Specific to leprosy
Timescale	3 years
Deliverable	Improved early nerve impairment detection and optimal treatment
Key investigators	TENLEP group
Status	Funded
Estimated costs	£1,000,000

Improved treatment for ENL Reactions	**Evaluate effectiveness**
Problem	ENL reaction is a common complication in MB patients with high bacteriological indices
Importance	ENL is a widespread, chronic complication affecting quality of life
Objective	Develop improved treatment
Activities	Clinical trials
Relationship to NTDs/MDGs	Specific to leprosy
Timescale	5 years
Deliverable	Reduce morbidity by better ENL treatment
Key investigators	Lockwood, Sundar Rao
Status	Part funded
Estimated costs	£1,000,000

5. Prevention of disability

Integration of national programmes (Legs to stand on)	**Technology transfer**
Problem	Prevention of disability activities are effective but coverage is very limited
Importance	Chronic, progressive disabilities are a problem for more than 3 million people after MDT completion
Objective	Increase coverage of POD activities integrated with other lower limb care in global programme
Activities	Implementation and integration of POD activities in 'Legs to Stand On' network
Relationship to NTDs/MDGs	Integration with lymphatic filariasis, Buruli ulcer and other conditions such as diabetes
Timescale	5 years
Deliverable	Better access to effective, integrated lower limb care for people affected by leprosy
Key investigators	ILEP, Cross, Post, NTD Collaborators
Status	Not funded
Estimated costs	£2,000,000

Test novel treatment for plantar ulcers	**Evaluate effectiveness**
Problem	Plantar ulcers are a common and chronic problem for many patients after completing MDT
Importance	Plantar ulcers cause morbidity for people affected, use a high proportion of clinical service and surgery, and require specialised footwear
Objective	Test new treatments for plantar ulcers
Activities	Clinical trials
Relationship to NTDs/MDGs	Relate to other lower limb care
Timescale	5 years
Deliverable	Improved quality of life and reduced morbidity through better management of plantar ulcers
Key investigators	ILEP
Status	Not funded
Estimated costs	£500,000

6. Community-based rehabilitation

Increase participation in CBR	Technology transfer
Problem	A proportion of people affected by leprosy need rehabilitation but have limited access
Importance	Rehabilitation for some people affected by leprosy is necessary to improve quality of life and participation in society
Objective	Increase access and participation in CBR
Activities	Activities to promote participation of people affected by leprosy in CBR programmes
Relationship to NTDs/MDGs	Common issues with other disabling conditions
Timescale	5 years
Deliverable	Improved quality of life by Increased participation of people affected by leprosy in CBR
Key investigators	WHO, ILEP, IDEA, IDDC
Status	Not funded
Estimated costs	£500,000

Test CBR guidelines	Evaluate effectiveness
Problem	Comprehensive guidelines for CBR have been published in 2011
Importance	Access to effective CBR is important for a proportion of people affected by leprosy to improve their physical and social functions
Objective	Test effectiveness of CBR guidelines in field
Activities	Implementation of guidelines in pilot studies
Relationship to NTDs/MDGs	Relates to all disabling conditions
Timescale	5 years
Deliverable	Evidence of effectiveness of CBR guidelines
Key investigators	WHO, UN, ILEP, IDDC
Status	Not funded
Estimated costs	£3,000,000

7. Stigma reduction and advocacy

Implementation	Technology transfer
Problem	Stigma associated with leprosy affects the physical and social function of those affected
Importance	Stigma is a major constraint for all those affected by leprosy and their families
Objective	Application of community activities to change attitudes to leprosy
Activities	Implementation of interventions proven to be effective in reducing stigma
Relationship to NTDs/MDGs	Stigma is relevant to many NTDs and HIV/AIDS
Timescale	5 years
Deliverable	Improve social participation through reduced stigma associated with leprosy
Key investigators	ILEP, IDEA
Status	Not funded
Estimated costs	£2,000,000

Test interventions to reduce stigma	Evaluate effectiveness
Problem	Stigma associated with leprosy affects the physical and social function of those affected
Importance	Stigma is a major constraint for all those affected by leprosy and their families
Objective	Develop and test interventions to reduce stigma in different country settings
Activities	Intervention trials
Relationship to NTDs/MDGs	Stigma is relevant to many NTDs and HIV/AIDS
Timescale	5 years
Deliverable	Tools proven to reduce stigma to increase quality of life in different country settings
Key investigators	ILEP, IDEA, van Brakel
Status	Partially funded
Estimated costs	£3,000,000

Translate and disseminate UN Guidelines	Technology transfer
Problem	There are laws and regulations in many countries that discriminate against leprosy
Importance	This is a human rights issue for leprosy
Objective	Advocate for change based on new UN guidelines on leprosy discrimination
Activities	Translate, disseminate and advocacy
Relationship to NTDs/MDGs	Discrimation applies to all NTDs and HIV
Timescale	3 years
Deliverable	Change in legislation and regulation on discrimination to improve social participation
Key investigators	ILEP, IDEA,UN
Status	Not funded
Estimated costs	£500,000

Test Charter approach	Evaluate effectiveness
Problem	People affected by leprosy are discriminated against and are not aware of their human rights
Importance	Loss of rights of people affected by leprosy affects individuals and society
Objective	Develop and promote a charter for people affected by leprosy
Activities	Develop charter based on those available for other conditions and test this with people and society in a number of countries
Relationship to NTDs/MDGs	Patient charters are relevant to all NTDs
Timescale	3 years
Deliverable	Empowerment of those affected by leprosy through a Charter of rights for people affected by leprosy
Key investigators	ILEP, IDEA, UN
Status	Not funded
Estimated costs	£500,000

8.Health/Social Care Integration

Integration of health and social care	Technology transfer
Problem	Leprosy programme on their own are unsustainable at low levels of endemicity
Importance	Leprosy must be integrated with other health and social care programmes to be cost-effective and sustainable
Objective	Implement leprosy services integrated with primary health care, dermatology, CBR and NTD programmes
Activities	Develop links with primary care, dermatology, CBR and NTD programmes to ensure that leprosy services are fully included
Relationship to NTDs/MDGs	Closely linked with all NTDs
Timescale	5 years
Deliverable	Delivery of leprosy care in low endemic settings with primary health care, dermatology, CBR and NTD programmes
Key investigators	Government NPM, ILEP, NTD, dermatologists, and CBR programmes and other NGOs
Status	Not funded
Estimated costs	£500,000