Editorial

Dear Friends,

It is always a pleasure to share with our well wishers and collaborators news of the happenings in the Research & Training Domain of The Leprosy Mission Trust India.

We are happy to welcome our new Executive Director Dr Mary Verghese, as she took over the responsibility for The Leprosy Mission Trust India from March 21, 2017. We publish a message from her addressed to all our readers.

This issue brings you two articles by Dr Ruth Butlin with her extensive experience in leprosy. The first article, on alternative regimens for the treatment of leprosy, discusses two studies on the topic and the rationality of the WHO recommendation. The second is an interesting article on the research funded by the Leprosy Research Initiative and The Leprosy Mission’s involvement in research funded by the organisation. It is an encouraging read.

Mallika Lavania is a Senior Research Scientist in the Stanley Browne Laboratory, and she writes about the development of a rapid and affordable assay testing for drug resistant strains of *M. leprae* in leprosy patients on treatment. This would help us to monitor emergence of resistance and enable early intervention to avoid its onward transmission.

Apart from this, there is a collection of abstracts which we hope will be of interest, and a brief report on the main events so far this year.

Happy Reading!

Annamma S. John
Editor & Head (Research & Training)

Message from the Executive Director

Dear Friends,

It is a privilege for me to write a message for this issue of the Research and Training Newsletter. We have focussed on research in leprosy over the past few years in basic, clinical, and operational research. This has generated interest amongst our colleagues to engage with research and develop a spirit of enquiry. We are delving into unanswered questions on early diagnosis, transmission, reactions and drug resistance in our attempt to defeat leprosy.

Over the years, we have generated a lot of evidence through our research. We need to see that these evidences are incorporated into policies and practices that will improve the quality of life of people affected by leprosy. We also need to continue research with much more focus so that it helps people affected by leprosy and their communities to transform their lives and live with dignity.

But we cannot do this alone. It is strategically advantageous for us to work with other groups and organisations with similar interests. The synergy that is created when we work collaboratively will result in greater accomplishments than when we work alone. The sharing of resources and expertise will help us to achieve more.

Our collaborative work so far has produced significant results. I’m sure, together we can achieve more!

I wish all our readers the best as we together become a learning organisation with the support of all our well wishers.

Dr Mary Verghese
Executive Director
The Leprosy Mission Trust India
Alternative drugs for leprosy

Recently, in the Indian Journal of Leprosy there were 2 interesting papers from Karigiri (by the same group of authors): samples from leprosy patients’ lesions had been inoculated into mice to test the sensitivity of the M. leprae to individual drugs or combinations of drugs. There are two similar papers, one concerning samples from newly diagnosed cases, and one on samples from a case known to have rifampicin resistant bacteria; both papers are quite hard for a field worker to read. There are two interesting papers from Karigiri (by the same group of authors): samples from leprosy patients’ lesions had been inoculated into mice to test the sensitivity of the M. leprae to individual drugs or combinations of drugs. There are two similar papers, one concerning samples from newly diagnosed cases, and one on samples from a case known to have rifampicin resistant bacteria; both papers are quite hard for a field worker to read as there is so much technical detail. Of course, it is necessary for laboratory scientists to include all this information about methodology and bacterial growth in such a paper.

In the first paper (“Evaluation of antibacterial drugs and their combinations in a murine model …..”) the authors report on experiments with samples from newly diagnosed leprosy cases with BI >= 3+, who were seen at Schieffelin Institute of Health Research and Leprosy Centre (SIHR&LC). These samples had been checked by genome sequencing to confirm they did not have the mutations for resistance to individual drugs of the standard WHO MDT regimen. It is not clear how many patients gave samples, nor whether they were all local people. Drugs tested individually were clarithromycin, rifapentine, minocycline, moxifloxacin and ofloxacin. Combinations were as in the box below. Both daily and intermittent (monthly) regimen were tried. The results showed that rifampicin or rifapentin or moxifloxacin individually were highly effective in daily or intermittent dosages with little difference between them. Looking at the 5 combinations, they found that EITHER clarithromycin & minocycline OR minocycline & ofloxacin, together with either rifampicin or rifapentine, were effective. They conclude that the standard WHO MDT regimen is still the best option for leprosy infections with drugs sensitive to the 3 component drugs. Replacing rifampicin with rifapentin or with moxifloxacin does not improve efficacy.

They suggest that if a shorter regimen is needed, based on these results the best regimen to try would be monthly rifampicin, ofloxacin, minocycline (OR monthly rifampicin, clarithromycin, minocycline – but clarithromycin is much more expensive and has more adverse effects). Moxifloxacin should be kept aside for managing rifampicin resistant cases so should not be included in standard treatment. “Monthly ROM* therapy” has been used in small scale clinical studies and deserves further investigation.

In the second paper (Evaluation of antibacterial activity… in the murine model of rifampicin resistant leprosy), a sample was obtained from a leprosy case who had a BI of 3+ having relapsed 3 years after completing standard WHO MB MDT regimen at their centre. This sample contained M. leprae resistant to rifampicin as demonstrated both by mouse foot pad technique and by molecular methods (which identify the characteristic mutation at rpoB gene associated with rifampicin resistance). The same drugs, singly and in various combinations, with daily doses and intermittent dosages, were tested as in the other paper. They concluded that the best treatment regimen was standard WHO MB MDT and if rifampicin needed to be replaced, then next best regimen would be Clarithromycin and minocycline and moxifloxacin (CMM) as a daily regimen.

It sounds strange that the rifampicin, clofazimine and dapsone regimen, as the patient received before, should be optimal first choice for a proven rifampicin resistant case. Part of the reason is the high level antibacterial effectiveness of the clofazimine-dapsone combination. In the real life situation (where one usually does not have results of lab testing for drug resistance immediately available) another factor in choosing this regimen is that some “relapse patients” did not take the full doses regularly for the full duration when given their first course of MDT.

This study supports the WHO recommendation to use a second course of standard MB MDT as first line treatment for any relapse case.

*ROM is familiar to some from its use as single dose therapy for single skin lesion (smear negative) leprosy, but the rifampicin-ofloxacin-minocycline combination as monthly dose is also an option for people who cannot or will not take clofazimine

3. D N Lockwood, M Da G Cunha 2012, Developing new MDT regimens for MB patients to test ROM 12 month regimen globally. Leprosy Review 83, p241-244
4. WHO 8th expert committee report, 2012, technical report series 968

Dr C Ruth Butlin
News & Events

The Leprosy Mission Trust India Research Committee (TLMTIRC)

The TLMTIRC was held at TLMTI Country office on February 25, 2017. It was a well-attended and fruitful meeting. Two experts who will be joining the committee were invited to participate in the session. Dr Pushpendra Singh, Assistant Professor and Ramalingaswami Fellow in the Department of Microbiology and Biotechnology Centre of The Maharaja Sayajirao University of Baroda, Vadodara, who has previous experience in leprosy, and Dr Ambarish Dutta, Associate Professor, Indian Institute of Public Health, Bhubaneshwar, an expert in Epidemiology and Public Health, who has also worked in leprosy and TB earlier. Six new proposals, on topics ranging from management of disability, social participation, and isolation of environmental mycobacteria to understand transmission were submitted for review.

Training Workshops

This year we have already had two Training Workshops, both organised by the Health Domain to enhance the skills of our doctors.

The first, on Ulcer Management, for TLMTI Medical Officers, was held from March 7 – 10, and the second was between May 9 – 12, at TLM Hospital, Purulia. Ten participants attended the first workshop, while thirteen attended the next one. The workshops were participatory and practical, with theory and hands on training in ulcer care. The topics were wound healing, causes of ulcers, prevention of ulcers, classification and management of ulcers, other foot problems in leprosy, podiatry in leprosy, physio therapeutic assessment of leprosy and footwear prescription in leprosy. Opportunities were provided for hands-on work in debridement of ulcers and administration of regional anaesthesia.

The Spring Meeting of Leprosy Research Initiative

This Annual Review meeting was held at Van Der Valk Hotel, Veenendaal, The Netherlands on April 6–7, 2017.

Akshya Nayak participated in the meeting to report on a study, A comparison of three types of targeted, community-based health education aimed at promoting early detection, supported by LRI. The progress made in the study was presented and experiences shared with representatives from other projects funded by LRI from many countries. A detailed report on this meeting can be found on page 6.

Stanley Browne Laboratory Scientific Advisory Committee

This meeting which is held once a year, was held on April 25, 2017 at the Country Office at CNI Bhavan, New Delhi. The work done during the past year on ongoing projects and published papers was reviewed and appreciated. The meeting was enriched and enlivened by the animated discussions arising from the perspectives of clinicians such as Dr. Loretta Das and the scientists working in basic sciences.

Two new proposals were reviewed:

- Study to identify possible underlying mechanisms for emergence of the resistance in Mycobacterium leprae strains in India by Whole Genome sequencing, and
- A Cohort Study to Understand Focal Transmission of Leprosy in Multi-case Families from Endemic Regions in Purulia, West Bengal.

Translational Immunology – Bench to Bedside
Dr Itu Singh and Mr Vinay Pathak attended a symposium organised by Department of Biochemistry, AIIMS & Indian Immunology Society on “World Immunology Day”, April 29, 2017. The Symposium was held at Teaching Block, AIIMS, New Delhi. The theme of the symposium was “Translational Immunology – Bench to Bedside”. The Chief Guest of the symposium was Prof G. P. Talwar, and Guest of Honour was Prof Randeep Guleria (Director, AIIMS). There was a lecture on Therapeutic monoclonal antibodies by Dr S.K. Gupta (NII).

Abstracts

Uniform multidrug therapy for leprosy - time for a rethink?

Uniform multidrug therapy (U-MDT) is a single regimen for all cases of leprosy, lasting for six months. It was first discussed as a serious proposition at the WHO Technical Advisory Group in 2002 and an Editorial in 2003 laid out several criticisms of the concept. The main criticism was that it added an unnecessary drug to the current paucibacillary (PB) treatment, while undertreating multibacillary (MB) cases, especially those with a high bacteriological index. Important considerations when discussing MB cases were that very little evidence was available at that time concerning the efficacy of 12 months treatment (introduced in 1998), or about the level of rifampicin resistance that could potentially be developing undetected in leprosy patients on MDT. If significant rifampicin resistance was developing, it would be unwise to attempt further shortening of the regimen.

Widespread borderline tuberculoid leprosy with HIV co-infection
Kechichian E1, Tomb R2., Lancet Infect Dis. 2017 Mar;17(3):348

A 35-year-old Lebanese man who had previously lived in Oman for 4 years presented to the outpatient clinic of the Hôtel Dieu de France hospital, Lebanon, with a generalised eruption of annular plaques. 4 years previously he had consulted our clinic for ill-defined ulcerated plaques associated with low-grade
fever and general status alteration. At that time, eczema, secondary syphilis, and vasculitis were all considered during differential diagnosis. A skin biopsy, serological testing for syphilis (Treponema pallidum haemagglutination assay and Venereal Disease Research Laboratory test), HIV 1/2 enzyme immunoassay, and a recombinant purified protein derivative (PPD) test for tuberculosis were ordered along with a complete blood count and liver and renal function tests.

Achieving Integration through Leprosy Case Detection Campaign (LCDC)

V C Giri, V M Bhagat, S R Bavisar, Showkath MK Ali; IJBR; 8 (1), 38-41. DOI: http://dx.doi.org/10.7439/ijbr.v8i1.3832

Leprosy is chronic infectious disease, mainly affects skin and peripheral nerve, caused by M. Leprae. In India, 58% of global new leprosy cases were detected annually. Due to the passive case detection, large numbers of cases are hidden in community, leading to more deformity. After integration of NLEP in to General Health Care, the involvement was not satisfactory. Leprosy Case Detection Campaign (LCDC) is a novel concept launched by Central Leprosy Division, Dt. GHS, Government of India, in fifty districts of seven states having Prevalence Rate 1 to 1.32 / 10,000 populations. This activity by house to house case search by using ASHAs (Accredited Social Health Activist) and Male Volunteer and IEC (Information Education Communication), on line of Pulse Polio Campaign. Pre-activity meeting of all stake holder at state, district and block level were conducted. Training of Medical Officers and Supervisors were conducted at district level. ASHAs and male volunteers were conducted at block level by Medical officers. The programme has in built mechanism monitoring at District, Block and PHC level to insure maximum participation and desire outcome. Five districts of Maharashtra around 8340940 populations visited by LCDC teams and found 8553 suspects. On examination of suspects by Medical officers 166 (101 MB, 65 PB) new Leprosy patients were identified in this campaign. The campaign was mainly able emphasis importance of active case search in leprosy and awareness in general population through IEC.

Leprosy Continues to Occur in Hilly Areas of North India


Background: The aim of present study was to describe the profile of leprosy patients attending the outpatient department of dermatology in tertiary care hospital in Srinagar, Uttarakhand, North India.

Methodology: This descriptive retrospective study. Patient data at the time of diagnosis were retrieved onto a presdesigned proforma, which concerned the following variables at the time of registration: age, sex, and residence. Newly registered outpatients leprosy cases between 2009 and 2014 were included in the study.

Results: It was found that 65 were multibacillary leprosy cases. Males constituted 62.8% of all leprosy cases. The majority (83.7%) belonged to the age group of 18-60 years. Of the total 48.8% of the new leprosy cases were from the Pauri district. The leprosy incidence rate in this population was 2.71 per 1000 patients.

Conclusion: Leprosy still continues to be a communicable disease of concern. The lower incidence in women and children provokes the need to strengthen contact screening, early case detection, and referral activities in the population to sustain elimination.

“I Wasted 3 Years, Thinking It's Not a Problem”: Patient and Health System Delays in Diagnosis of Leprosy in India: A Mixed-Methods Study

ThirumugamMuthuvel, Srinivas Govindarajulu, PetrosIaakidis, Hemant Deepak Shewade, Vasudev Rokade, Rajbir Singh, Sanjeev Kamble


Background: Worldwide, leprosy is one of the major causes of preventable disability. India contributes to 60% of global leprosy burden. With increasing numbers of leprosy with grade 2 disability (visible disability) at diagnosis, we aimed to determine risk factors associated with grade 2 disability among new cases and explore patients and providers’ perspectives into reasons for late presentation.

Methodology / Principal Findings: This was an explanatory mixed-methods study where the quantitative component, a matched case-control design, was followed by a qualitative component. A total of 70 cases (grade 2 disability) and 140 controls (grade 0) matched for age and sex were randomly sampled from new patients registered between January 2013-January 2015 in three districts of Maharashtra (Mumbai, Thane and Amaravati) and interviewed using a structured close ended questionnaire. Eight public health care providers involved in leprosy care and 7 leprosy patients were purposively selected (maximum variation sampling) and interviewed using a structured open-ended interview schedule. Among cases, overall median (IQR) diagnosis delay in months was 17.9(7–30); patient and health system delay was 7(4–16.5) and 5.5(0.9–12.5) respectively; this was significantly higher than the delay in controls. Reasons for delayed presentation identified by the quantitative and qualitative data were: poor awareness of leprosy symptoms, first health care provider visited...
being private practitioners who were not aware about provision of free leprosy treatment at public health care facilities, reduced engagement and capacity of the general health care system in leprosy control.

**Conclusion:** Raising awareness in communities and health care providers regarding early leprosy symptoms, engagement of private health care provider in early leprosy diagnosis and increasing capacity of general health system staff, especially targeting high endemic areas that are hotspots for leprosy transmission may help in reducing diagnosis delays.

### Rapid and affordable assay for drug resistant strains of *M. leprae*

Leprosy is a poverty related disease with multidimensional consequences. The emergence of drug resistance and genetic mutation in *M. leprae* is a serious threat at a time when dramatic decline in prevalence and new case detection have been achieved by concerted chemotherapy interventions of the National Leprosy Eradication Program and its global partners. Multi Drug Therapy is the mainstay of leprosy control programs. If emergence of mutation is not controlled with alternative drug regimens, eradication measures with chemotherapy will be completely defeated.

Therefore a surveillance mechanism is needed which should function as a watchdog for appearance of drug resistance in-country; rapid detection and control of drug-resistant strains is essential for countries approaching leprosy elimination levels. To monitor transmission dynamics of drug resistant leprosy, genome-wide sequencing and comparison of *M. leprae* strains by whole genome sequencing (WGS) of strains from drug resistant patients can reveal specific polymorphisms associated with resistance. WGS can detect specific signatures of disease presentation and progression among relapsed cases. This will aid in understanding transmission and the possibility of compensatory mutations related to resistance between the strain and the endemcity.

Rapid testing for drug resistance in patients on treatment can monitor emergence of resistance and enable early intervention to avoid its onward transmission, infecting new individuals.

SB Lab has been working in the areas of drug resistance for the past 8 years as part of the WHO Sentinel Surveillance Study on Drug Resistance in Leprosy and has already recorded the emergence of resistance against DDS, Rifampicin and Ofloxacin from TLMTI hospitals around the country. We have performed mouse foot experimentation to check whether novel mutations in rifampicin drug are conferring resistance or not. We have screened all these resistant cases for further analysis.

The study described above will aid in developing a rapid and affordable assay testing for drug resistant strains of *M. leprae* in leprosy patients on treatment. Early testing of resistant strains will also help us to monitor emergence of resistance and enable early intervention to avoid its onward transmission.

**Dr Mallika Lavania**  
Research Scientist  
Stanely Browne Laboratory

### LRI-funded research projects in cooperation with TLM

At the recent Leprosy Research Initiative spring meeting (6th -7th April 2017), recipients of LRI grants presented progress reports on their studies. Out of 20 presentations half the studies were being carried out by, or with help of, TLM centres. There was an amazing variety of problems being investigated, their only feature in common being some reason to believe results could eventually help people affected by leprosy. And an amazing variety of approaches are being used by diverse teams of investigators, located in many different countries.

The Leprosy Research Initiative (LRI) was established after the International Leprosy Congress at Brussels in 2013. It aims to facilitate funding of leprosy-related research, and each year since 2014 has invited Letters of Intent from people/organisations with good ideas for research studies. From amongst these letters of intent submitted, the most promising are selected. Their authors are then invited to send in full proposals and about half of these will be offered grants for up to 3 years’ work. More information is available at [www.leprosyresearch.org](http://www.leprosyresearch.org)

I was fortunate to be present as an “extra participant” at the workshop and was very impressed to see the quality of the on-going work and the potential it had to improve the situation on the ground in the real world of meeting the needs of leprosy-affected people. I am sharing a few examples of studies in progress or recently completed.

**Leprosy control**

Erasmus University and rural health programmes...
of TLMBangladesh are engaged in a study of novel immunodiagnostic tools for detection of very early leprosy infections. Blood samples from contacts of leprosy cases, including those who themselves later develop leprosy, are assayed in Netherlands in an attempt to identify a “profile” indicative of sub-clinical or progressive infection.

Rural health programmes have also been doing a study of household contacts of about 16000 people diagnosed with leprosy over the past 20 years, to elucidate the temporal pattern of new cases arising amongst this most susceptible group of people. Results will provide evidence for best contact management policy.

TLMIndia centres collaborated in a study comparing three types of targeted community-based health education (training of non-formal leaders, motivating leprosy-affected people to examine their own contacts, or a general public awareness campaign) to see which was most effective in terms of enhancing early case detection.

Clinical issues

Three TLM centres (Purulia, Anandaban and DBLM hospitals) were involved in the *ENLIST* work on development & validation of a scale to measure severity of ENL reaction; this scale will facilitate clinical trials and preparation of guidelines for patient management.

At TLM’s Mycobacterial research laboratory in Nepal, a fascinating study is in progress looking at the effect of helminth infestation on the immunology & clinical manifestations of leprosy.

From Karigiri came a study on molecular biology “signatures” which might help in determining onset of reactions.

The “Community programme” under TLM Bangladesh undertook a study of pressure-reduction properties of footwear (comparing selected commercially-available footwear with custom-made MCR-insole footwear), using both sensitive objective measures and a cross-over trial of ulcer incidence in people wearing the test footwear.

The “burden of treatment” is the subject of a study undertaken by TLMMyanmar, in collaboration with Griffith University (Australia). There is a need to better understand the nature and size of this “burden” carried by leprosy-affected people, and to find ways to assess it (with a long-term view to either reduce the burden or to increase carrying-capacity).

Public attitudes

TLM Nigeria investigated the role of Christian churches (leadership and members) in leprosy and disability-related stigma: an important issue to consider in many other countries!

Working with IDEA*, TLM staff are also investigating the use of UN principles and guidelines in local participatory campaigns to increase dignity & empowerment – this project is to be carried out in 3 African countries but results are so far available only from Niger.

Besides the presentations of LRI-funded studies, we were treated to interesting presentations by invited speakers on leprosy as a model for understanding the molecular basis of common diseases, on results of a modelling project on preventative interventions for leprosy control, and on the attributable impact of community based rehabilitation. On the second day of the workshop each participant was invited to attend any 2 of 4 interactive sessions, one of which was on future development of LRI policy. There was a good discussion including on the selection of priority areas. Another session was about implementation of research results: what are the barriers hindering application of laboratory findings in the field?

We can be proud of what TLM is currently contributing to leprosy research, but many unanswered scientific questions remain. Anyone who feels challenged to attempt a study would do well to start thinking now about preparing a letter of intent to send to LRI early next year!

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**ENLIST**= ENL International Study Group  
**IDEA**= Association for Integration, Dignity and Economic Advancement (of leprosy-affected people)

Dr C Ruth Butlin