Editorial

Dear Friends,

Another year has flown past!

As we approach the end of the year, we look back and take stock of how we have used the time, and what we have been able to achieve on our journey towards the eventual eradication of leprosy. Though the individual steps taken may not have been very large, each step takes us further as we build up evidence and find answers to the age old problem of leprosy.

This issue of the Newsletter brings a message from our Executive Director who has provided great impetus to Research in TLMTI during the last few years, encouraging us to keep up our efforts and work to optimise our research as a cross-cutting activity in different disciplines and areas of the work. Dr Puspendra Singh explains the scope of basic sciences research in the field of leprosy in his article. Dr. Ravindra Turankar tells us briefly about the significance of finding viable leprosy bacilli in the environment. We have selected three abstracts that touch on subjects which are of interest to all of us: stigma, leprosy trends at a referral centre, and the proposal of a study on the much discussed LPEP campaign.

As Christmas approaches, the team in the Research & Training domain wishes you a joyful Christmas and a Blessed New Year.

Hope you enjoy the Newsletter.

With warm wishes,

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

Message from the Executive Director

It is a privilege to be writing a message for the year’s last issue of the Research and Training Newsletter. It gives us an opportunity not only to look back at the year, but also to review the past five years and see how we have moved as an organization in establishing ourselves as one of the leaders in leprosy research in the country.

At the start of our first country strategy in 2011, we decided to work towards changing our attitude and approach to research. Till then we felt that research was a specialised activity that needed more than ordinary skills. In our quest to become a learning organization, we looked at research as one of the areas that would help us achieve that, and we have done so to an extent. We started by working towards making research a day-to-day activity, and developing and sustaining a research culture in the organization that was a lot different from the past: a culture of asking questions, finding answers and applying them where they matter most – in changing the lives of those affected by leprosy.

Looking back, I am happy that we have certainly made huge strides in establishing a research culture in TLMTI that is very different from the one that existed before. Research has become a significant part of our learning culture and is accepted as a day-to-day activity. This is reflected in the quality and extent of research that is conducted in TLMTI. And, in the process, we have established ourselves as an organization that can become a research leader in leprosy, gaining credibility through the many awards our staff has received nationally and internationally.

Considering the amount of experience, expertise, material, and skilled and enthusiastic people we have in TLM India, however, we have not yet maximised the potential to lead leprosy and related research from the front. Unless we capitalise on our strengths, sustain the
After implementation of multidrug therapy for more than three decades there has been a significant drop in prevalence of leprosy; however, new cases are appearing at the same rate and therefore the annual new case detection rate (ANCDR) has remained almost the same for the last ten years. It is believed that, as humans are the only natural host, case finding and timely treatment of patients will automatically bring down the number of new cases in the community, but unfortunately this does not appear to be happening. Furthermore, operational factors like shortening of treatment duration, use of point prevalence as an indicator could have contributed to the sharp decline in prevalence. This raises the question of the possibilities of human carriers and sub clinically infected individuals as possible reservoirs of infection. But, in addition to this, an extra-human reservoir could also be possible. *M. leprae*, being an obligate intracellular parasite, cannot be cultured in any artificial culture media, but it has been shown to reside in wild armadillos in North America.

Various earlier studies indicate that environmental nonhuman sources could be critical to human infections with *M. leprae*. Scientist reported that *M. leprae* discharged through secretion from patients (coughing and sneezing) may get air-borne as *M. leprae* droplets settle both in soil and water and may cause infection. Further, proof of air-borne infection and nasal route of entry was established from the experiments carried out in thymectomized and whole body 900r irradiated (immunodeficient) mice by infecting them by *M. leprae* aerosol through respiratory route.

Although there is a considerable experimental evidence supporting the entry of bacilli into a new host by invasion, and subsequent infection though the nasal mucosa or abraded/punctured skin, very little information is available regarding the survival of bacilli outside the host (environment). However, recently uptake of *M. leprae* by Acanthamoeba castellanii was reported in laboratory experiments under laboratory conditions. It was showed that *M. leprae* can survive inside the parasite up to the cystic stage of *A. castellanii*. (Lahiri and Krahenbuhl 2008).

Research scientists at the Stanley Browne Laboratory, using advanced molecular technology called polymerase chain reaction (PCR), which identifies minute quantities of *M. leprae* DNA, observed high PCR positivity samples of soil (218 out of 700; 31%) and water (73 out of 400; 18%) from areas of patients in endemic villages. These samples when further screened for *M. leprae* viability, and it was observed that 106 soil (15%) and 34 water (8%) samples showed presence of 16S rRNA gene target (Viability marker) of *M. leprae*. (The presence of 16S rRNA is indicator of viable bacteria which is present in samples). By using molecular methods we also observed 29% of soil and 22% of water samples were PCR positive for *A. castellanii*. Further, we are now engaged in developing fluorescence based in-situ hybridization technology for confirmation of the presence of viable *M. leprae* within viable amoeba isolated from natural pond water and soil around inhabiting areas of leprosy patients.

This study will help us to prove association of *M. leprae* with protozoa in natural environmental conditions. If *M. leprae* are found alive inside protozoa, then it will be definite that these protozoa species are acting as reservoir for *M. leprae* in the environment in endemic regions and may also be responsible for transmission of leprosy. Hence the present study has been developed to look at the possible presence of viable *M. leprae* inside amoeba species in the environment and other associated factors that could play a role in exposure and transmission.

**Dr Ravindra P Turankar**
Research Scientist
Stanley Browne Laboratory
Significance and scope of laboratory research in the eradication of leprosy

Leprosy control programmes have been a tremendous success. However, the over-projection of this success and the aftermath of self-congratulatory celebrations have bred complacency in the general public and policy makers alike. Today, leprosy (or Hansen’s disease) is widely considered as a very rare disease by many people. However, when these people are told the reported statistics of leprosy new case detection (that there are still over 200,000 new cases being recorded globally each year, and perhaps many more which go unrecorded), it comes as a big surprise to them. Today, the majority of leprosy cases (~95%) are found in just 20 countries, most of which are in South East Asia. However, today’s world is a global village where international travel and migrations are getting more and more frequent. Hence, despite its rarity in the western world (particularly Europe and North America), research on leprosy is considered important and several research groups have made notable discoveries in basic as well as operational research. Some of the important areas of leprosy research are being discussed in this article.

Early diagnosis: Differential diagnosis of leprosy poses great difficulties in some cases, especially due to declining clinical expertise (1, 2), as its symptoms sometimes might appear very similar to other dermatological conditions. Leprosy is therefore sometimes referred to as the great imitator (3-5). Further, the lack of awareness among physicians, particularly in low-endemic settings, often leads to diagnostic delays, contributing to serious neurological consequences (6-9). Hence, a major priority of current leprosy research is to develop a laboratory test that can aid in accurate identification of leprosy at an early stage, to prevent disabilities and M. leprae transmission. Further, episodes of reactions can pose additional challenges, as this requires specialized expertise. Hence, the focus of several research projects is on identification of biomarkers of nerve damage and reactions (10). These studies investigate host gene expression, either targeting a few candidate genes by qPCR or by analyzing whole transcriptional profiles using microarray or RNA-sequencing.

Surveillance of Drug resistance, molecular diagnostics and testing of new drugs: Currently available multidrug therapy is very effective and very few cases of drug resistant M. leprae are reported. However, careful monitoring of the trends has been one of the key priorities for the World Health Organization. High Resolution Melting (HRM) analysis for molecular drug susceptibility testing (MDST) and genotyping has been developed which can be useful for the settings where DNA sequencing facilities are not available (11). New diagnostic antigens based upon recombinant fusion proteins have been recently developed for sensitive serological diagnosis (12). Quantitative PCR based enumeration of M. leprae (13) and determination of its viability using molecular assays (14) has also become available.

Viable M. leprae as a research reagent: Availability of viable M. leprae as a research reagent through National Hansen’s Disease Program (NHDP) has also accelerated testing of anti-leprosy compounds using radio-respirometry technique (15). These viable bacilli have been an invaluable resource to test the mechanisms of nerve invasion. A landmark paper describing the ability of cellular reprogramming of adult schwann cells into stem cell-like cells was also described which has attracted attention and appreciation from diverse fields (11). Similarly, investigations into neuropathogenic potential of M. leprae and the mechanisms by which it causes damage to the peripheral nerves is also a key priority. This also has implications for other forms of peripheral neuropathies: for example, diabetic and HIV-related neuropathies, which affect several hundreds of millions people worldwide.

Newly identified species M. lepromatosis: This species of leprosy bacilli, was described in a patient of Mexican origin in 2008 (16), and recently the draft whole genome of this bacterium was described (17) using Illumina Next Generation Sequencing which shows that both M. leprae and M. lepromatosis underwent reductive evolution together and then diverged ~ 14 million years ago. Despite a very deep divergence, they have very similar genome architecture and both remain uncultivable. Interestingly, this species was reported from red-squirrels in Scotland (18) which has raised several speculations of additional animal/environmental reservoirs of leprosy bacilli. However, more investigations are required in this matter.

Zoonotic leprosy: Role of armadillos in zoonotic spread of leprosy in southern United States was also confirmed by genome-scale identity of animal and human derived strains recently and hence has been a priority area of research to undertake molecular epidemiological investigations into armadillo and human leprosy in the areas where natural infection of leprosy in armadillos is common. As the natural habitat of armadillo range in a big part of South America also, such investigations into their role in zoonotic spread of leprosy possesses immense relevance and such studies are being planned whose results will be informative.

Rodent reservoir of leprosy in United Kingdom: Another interesting aspect of leprosy animal reservoir, the recent reports of presence of leprosy bacilli (M. leprae and M. lepromatosis) in Red-squirrels in United Kingdom has come as a big surprise, and the fact these animals harbor the same strains of M. leprae which were identified from the whole genome analysis of medieval skeletons from England suggests that these
animals have remained as an environmental reservoir of leprosy for several centuries. It is noteworthy that leprosy has declined from UK and most of the Europe after 16th century and there have been almost no human leprosy cases there for a few centuries. This poses a very pertinent question regarding the possible existence of some unknown animal reservoirs of leprosy bacilli in other geographic locations as well, specially in endemic countries. Hence, systematic investigations in this regard are urgently required, so that the stubbornly high rate of new case detection rate of leprosy in some of the hyper-endemic settings could be adequately investigated.

Cited literature:

12. M. S. Duthie et al., Clinical and Vaccine Immunology 14, 1400 (Nov, 2007).
16. X. Y. Han et al., Am J Clin Pathol 130, 856 (Dec, 2008).
18. A. Meredith et al., Veterinary Record 175, 285 (2014).

Author Biosketch

Pushpendra Singh completed his PhD in Drug Resistance mechanisms in mycobacteria from JALMA Institute (ICMR) Agra and then joined Prof. Stewart Cole’s group where his research focus was mycobacterial genomics. These studies provided evidence of zoonotic link of armadillos with leprosy in southern US. Subsequently, he contributed to the tracing the origin of this zoonotic strain to the medieval leprosy skeletons from Europe. These studies have been published in leading journals. Currently, as a Visiting Scientist, he has made leading contributions in establishing a fully functional Molecular Medicine Laboratory at the National Hansen’s Disease Program at Baton Rouge, Louisiana, USA where his primary research interest is to investigate the host-pathogen interaction and mechanisms of peripheral neuropathies using leprosy as a model disease.

Events

Ethics Committee meeting

TLMTI Ethics Committee met on 24th November at Delhi and considered three new research proposals. The proposals were:

- CSOs for Resource Mobilisation, Empowerment, Advocacy, Training & Employment, (CREATE),
- A comparison of the effects of computerised fabricated customised protective footwear using EVA and traditional customised protective footwear using MCR on the lives of patients with insensitive feet, multicentric trial and
- Genomic markers for pathological variants and transmission of leprosy bacilli.

The discussions were very useful, and the projects were approved subject to incorporation of the recommendations of the committee.

Curriculum Development Workshop

TLMTI is in the process of making its Training activities uniform. To facilitate this, a workshop was held to develop and standardise the curricula on leprosy and related clinical subjects such as NTDs, POID, Diabetes etc. for different categories of trainees, both internal and external. This workshop was held at TLM Hospital, Dayapuram from 1st to 3rd November, and was attended by experts from the fields of medicine, surgery, nursing, physiotherapy and occupational therapy.
Early Detection Project Review Meeting

The annual review meeting of the Early Detection project, which is being conducted in the states of Chattisgarh, Uttar Pradesh, and West Bengal, was held in Bhubaneshwar from 29th November to 1st December. The meeting was attended by the whole project team comprising field investigators and co-investigators from GLRA, NLR, and TLMTI. The progress made was monitored and plans for the next year were formulated.

Abstracts

🔗 The Impact of a Rights-Based Counselling Intervention to Reduce Stigma in People Affected by Leprosy in Indonesia.


Background: This paper assesses the impact of a counselling intervention on reducing leprosy-related stigma in Cirebon District, Indonesia. The unique features of this intervention are its rights-based approach, the underlying Cognitive Behavioural Therapy (CBT) model, the three types of counselling and the lay and peer counsellors who were involved.

Methodology/Principal Findings: Mixed methods (e.g. three scales, interviews, focus group discussions and reflection notes) were used to assess the impact of the intervention, which ran over a two-year period. There was a control area with no interventions. The study participants were people affected by leprosy and other key persons (e.g. family members). The sample size differs per method, for example, data regarding 67 counselling clients and 57 controls from a cohort, and notes from 207 counselling clients were examined. The notes showed that most clients faced stigma on a daily basis, whether internalized, anticipated and/or enacted. A significant reduction was found between the before and after total scores of the SARI Stigma Scale (p-value < 0.001), Participation Scale Short (p-value < 0.001) and WHO Quality of Life score (p-value < 0.001) among the counselling clients. While there is also an effect in the control group, it is much larger in the intervention group. Qualitative data indicates that knowledge and rights trigger change. Clients took steps to improve their life such as re-connecting with neighbours, helping in household activities and applying for jobs. Challenges include the wish to conceal their condition.

Conclusion/Significance: The findings show that the counselling intervention was effective in reducing stigma, promoting the rights of people with leprosy and facilitating their social participation. More research is needed on how to create a more sustainable intervention, preferably structurally embedded in the health or social services.
Leprosy trends at a tertiary care hospital in Mumbai, India, from 2008 to 2015.


Background: Leprosy remains an important cause of preventable disabilities. After the advent of multidrug therapy, new leprosy cases have come down dramatically. Despite this achievement, India, which contributes 60% of the global leprosy burden, faces some challenges to eliminate the disease, including active transmission in the community and delayed diagnosis of leprosy patients.

Objectives: The objectives of the study were 1) to determine sociodemographic and clinical characteristics of newly diagnosed adults and children (less than 15 years) with leprosy and their trends over time (2008-2015) and 2) to describe the profile of surgical procedures among leprosy patients registered for reconstructive surgeries during 2006-2015.

Design: Retrospective descriptive study was conducted involving a record review of new patients with leprosy registered in Vimala Dermatological Centre, Mumbai.

Results: A total of 578 new leprosy cases were registered in the hospital during 2008-2015. There has been a steady increase in the trend of child cases (less than 15 years) with leprosy and their trends over time (2008-2015) and x²=12.11, p<0.01. The majority of the patients (68%) were migrants of Uttar Pradesh and Bihar.

Conclusions: Targeting children and migrants and ensuring early diagnosis and treatment initiation are essential components for leprosy elimination in an urban metropolis in India.

Leprosy Post-Exposure Prophylaxis (LPEP) programme: study protocol for evaluating the feasibility and impact on case detection rates of contact tracing and single dose rifampicin.


Introduction: The reported number of new leprosy patients has barely changed in recent years. Thus, additional approaches or modifications to the current standard of passive case detection are needed to interrupt leprosy transmission. Large-scale clinical trials with single dose rifampicin (SDR) given as post-exposure prophylaxis (PEP) to contacts of newly diagnosed patients with leprosy have shown a 50-60% reduction of the risk of developing leprosy over the following 2 years. To accelerate the uptake of this evidence and introduction of PEP into national leprosy programmes, data on the effectiveness, impact and feasibility of contact tracing and PEP for leprosy are required. The leprosy post-exposure prophylaxis (LPEP) programme was designed to obtain those data.

Methods and Analysis: The LPEP programme evaluates feasibility, effectiveness and impact of PEP with SDR in pilot areas situated in several leprosy endemic countries: India, Indonesia, Myanmar, Nepal, Sri Lanka and Tanzania. Complementary sites are located in Brazil and Cambodia. From 2015 to 2018, contact persons of patients with leprosy are traced, screened for symptoms and assessed for eligibility to receive SDR. The intervention is implemented by the national leprosy programmes, tailored to local conditions and capacities, and relying on available human and material resources. It is coordinated on the ground with the help of the in-country partners of the International Federation of Anti-Leprosy Associations (ILEP). A robust data collection and reporting system is established in the pilot areas with regular monitoring and quality control, contributing to the strengthening of the national surveillance systems to become more action-oriented.

Ethics and Dissemination: Ethical approval has been obtained from the relevant ethics committees in the countries. Results and lessons learnt from the LPEP programme will be published in peer-reviewed journals and should provide important evidence and guidance for national and global policymakers to strengthen current leprosy elimination strategies.
# Publications from TLMTI in 2016

<table>
<thead>
<tr>
<th>Title of Paper</th>
<th>Authors</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASIC SCIENCES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CLINICAL SCIENCES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SOCIAL SCIENCES</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>