Dear Readers,

It is a pleasure and privilege to bring you the first issue of the Research & Training Newsletter this year. As usual, the months are flying by and as you will see in the ‘Events’ article, activities of the Research Domain are in full swing with project workshops and routine work. We are working with other domains to support research activities in field projects. The training activities will be focussing on developing and maintaining a high level of expertise in leprosy and related areas, and will be done in close collaboration with the Health and Sustainable Livelihoods & Empowerment Domain.

This year is an important year as we look forward to The International Leprosy Congress to be held in Beijing in September. TLMTI staff has submitted a number of abstracts and we look forward to a time of sharing and learning.

In this issue we bring you three articles. The first, by Dr. Ruth Butlin on post exposure prophylaxis for leprosy, which explains and explores the rationale of using BCG and Single Dose Rifampicin for post exposure prophylaxis. Another by Dr. Pim Kuipers on the “Bench to Basti” pilot study which tests a few innovative approaches to understanding what contributes to delayed diagnosis, and how earlier diagnosis might be achieved. The third article, contributed by Dr. U Sengupta, our Consultant at the Stanley Browne laboratory, is on Transmission, and helps us to understand where we are in our understanding of transmission in Leprosy during the Multidrug therapy (MDT) Era.

At present our research in TLMTI focuses mainly on transmission of leprosy, drug resistance, early detection / prevention of delay in diagnosis and stigma. Though funding for leprosy work and research is becoming more difficult to access, we are persisting with our efforts to avail of funding so that we can contribute to solving the issues confronting us.

We include a list of the publications of TLMTI staff during 2015. The topics covered range from pure science in SBL to disability issues and social aspects of ENL. If you would like more details about any of these papers please write to us.

We hope you enjoy this Newsletter and would be delighted to receive your comments, articles suggestions etc.

Happy reading!

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

PROMOTING EARLY DIAGNOSIS

A pilot study funded by the Leprosy Research Initiative has been underway in Chhattisgarh for a number of months and is now nearing completion. The “Bench to Basti” pilot study is testing out a few innovative approaches to understanding what contributes to delayed diagnosis, and how earlier diagnosis might be achieved. The study is based on the premise that delayed diagnosis is complex, and that many factors contribute. As a result, attempts to understand and respond to delay will have to accommodate that complexity, exploring the issue at many levels and from different perspectives. In response, the project has a number of unusual distinctives.

- First it is participatory. It has recruited and trained people affected by leprosy to be interviewers. They have conducted 39 interviews with people affected by leprosy, family and community members, exploring this problem. Initial indications are that these interviews have been very successful, identifying an array of factors.
• Second, the study is reflective. Initial interview results were taken to a number of reflection and discussion groups comprising different stakeholders, to obtain their interpretations and suggestions. Again, rather than limiting feedback to a few standardised responses, this step raised a host of important issues for exploration.

• Finally the study is also translational. Later stages of the research have taken the preliminary findings (from interviews and the reflection and discussion groups) and presented them to key stakeholders in senior positions, first to project managers in TLMTI and then to District Leprosy Officers in Chhattisgarh. The array of responses and ideas were presented to these people, and they were asked to identify which were potentially good suggestions and which were practical. They were also asked to prioritise key areas of focus in order to more effectively address delayed diagnosis.

While the responses are still being collated and analysed, it is clear that meaningful actions to prevent delayed diagnosis will have to be multifaceted. Beyond the key priority of awareness raising and education, these actions will have to include actively engaging communities and building local capacity. They should emphasise skilling and re-skilling service providers, as well as rethinking the systems and processes of service delivery, as well as other dimensions. Details will come in following months.

The WHO target for the elimination of leprosy, namely “Vigorous case finding and treatment would lead to global interruption of transmission by 2020.” is clearly important. The “Bench to Basti” pilot results indicate that there are also a number of other important and inter-related strategies which might promote earlier diagnosis (and help in interrupting transmission). A good way to understand these factors is through participatory methods. Further, an emphasis on translation will ensure that findings are more likely to be implemented.

Pim Kuipers, PhD
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Menzies Health Institute Queensland
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PROGRESS IN UNDERSTANDING TRANSMISSION IN LEPROSY DURING THE MULTIDRUG THERAPY (MDT) ERA

It is well known that leprosy is an infectious disease caused by *Mycobacterium leprae* and has adapted to humans from ancient times. However, it is the least infectious of all infectious diseases of mankind. In spite of being the least infectious, how is transmission still continuing in the community since biblical times? This has not been understood at all.

In western countries leprosy was widely prevalent during the medieval period. At that time there was no medicine available for treatment of leprosy and therefore segregation was the only procedure which was used by the community, leading to congregation of leprosy patients in one place called ‘Leprosy asylums’. Several ‘Leprosaria’ or leprosy hospitals were therefore founded in middle ages. In India the existence of leprosy has been documented since 2000 BC, and validated by archeological and molecular biological evidence. ‘Leprosy colonies’ evolved in India too as a result of segregation of leprosy afflicted individuals by their own family members and the community. However, in Europe the Industrial revolution during 18th and 19th centuries, transformed the then agrarian-rural based societies to industrial and urban types. Industrialization raised the standard of living and by the mid-19th century, industrialization was well-established throughout the western part of Europe and America’s northeastern region. This huge improvement in the standard of living brought about by industrial revolution led to a significant decline of leprosy prevalence in the West without the intervention of any drug. Today in the 21st Century, in spite of having an effective MDT, leprosy remains a public health problem in several countries in the world, including India.

Stanley Browne Laboratory (SBL) of TLMTI has therefore, in recent years been focusing on research in understanding the mechanism of transmission in leprosy. The research team visited the endemic villages in Purulia of West Bengal and Champa of Chhattisgarh and has investigated the biological samples (skin scrapings, saliva and nasal swabs) of patients and their contacts for the presence of *M. leprae* or its components. In addition, the common environmental material (water and soil) around leprosy patients’ homes and contacts have been investigated for the presence of *M. leprae*, which might possibly be serving as a continuous source of infection.

The preliminary results indicate that the environment is being contaminated with *M. leprae* through the nasal and oral discharges of leprosy patients. Nasal swabs of contacts of patients have been found to be positive for *M. leprae*. Further, presence of live *M.*
lepra has been found using molecular biological technique (16SrRNA) in the environment (soil and water of bathing and washing places) in these endemic villages. Hygiene and sanitation in most of these villages are very poor. There is no other source of water except the pond which is used for bathing and all other household purposes as seen below.

Further it was noted that M. leprae which are found in the patient and in the environment belonged to the same category/type. Hence, these environmental M. leprae might be acting as a source of infection to others.

It could be concluded from the present findings that environment might be playing a big role in transmission of leprosy. SBL is at present investigating whether M. leprae obtained from soil or water are capable of infecting mice.

Dr Utpal Sengupta
Consultant
Stanley Browne Laboratory

POST EXPOSURE PROPHYLAXIS FOR LEPROSY: CHEMO OR IMMUNE OR BOTH?

“Prophylaxis” is an intervention aimed at preventing clinical disease, and it is commonly done before the vulnerable subjects are exposed to infection: one gives measles vaccine before most children will encounter measles so that they already have protective antibodies, one tries to colonise people’s guts with (live) oral polio vaccine before the people encounter wild pathogenic polio viruses in their drinking water, or one starts taking anti-malarial drugs before entering a malarial area to discourage growth of the parasite if it is injected into you by a mosquito. These are examples of “pre-exposure prophylaxis”, which is often done, on a massive scale, as a public health programme for common infectious diseases.

For a few diseases (mostly where the incubation period is long) it is possible to do “post exposure prophylaxis” for selected individuals. A well-known example is with rabies: for those who have just been infected (usually from a dog bite) there is time to give anti-rabies vaccine and expect a protective immune response to develop before the rabies virus can cause clinical disease. Similarly during an epidemic of meningitis, household contacts of the newly diagnosed case (who may well have subclinical infection) can be given a single dose of a suitable antibiotic to protect them against Neisseria meningitides. Young children in a household containing an “open Tb case” receive isoniazid for a similar reason (but more than one dose!)

For leprosy what do we have available? In Brazil the authorities are sufficiently convinced of the value of BCG in combating leprosy, that they give a booster dose of BCG to household contacts of newly diagnosed leprosy cases, as part of the
national leprosy control programme (or a first dose if the person did not receive it as a baby). There is a fair amount of research evidence that BCG gives some measure of protection against leprosy, but on a wide scale no-one knows how much the millions of doses of BCG vaccine given over the years by national Tb control programmes have helped to reduce the incidence of leprosy!

The use of long-term dapsone as a prophylaxis for children in leprosy-affected households has a long history, but it is no longer recommended as a leprosy control measure. Despite evidence of giving some protection, the disadvantages outweigh the potential benefits. Single dose rifampicin (SDR) for household contacts of people recently started on MDT for leprosy (and hence no longer infectious) is a more recently introduced technique, for which there is good research evidence of effectiveness within the first 2 years. The rationale is that SDR treats “early infection” before any clinical manifestations are apparent. At present it seems unlikely that mass treatment (of whole populations) will be recommended for controlling leprosy although in some other diseases like filariasis this is effective (annual single doses of DEC for everyone living in the area, assuming many of them are in the subclinical stage of infection). Post exposure prophylaxis in leprosy is probably best targeted at those with highest risk, i.e. household contacts of known cases.

The subclinical cases of leprosy which are being “treated” are assumed to have a very small bacterial load; hence one drug given once is enough to prevent progression of the infection. However the SDR obviously cannot protect the individual from future infections with *M. leprae* which they may contract from other as-yetundiagnosed cases. Thus it is not surprising that the benefit of SDR does not last for long.

Would it be more beneficial to combine immune-prophylaxis (with BCG) and chemoprophylaxis (with SDR) for both a quick and prolonged effect, than to use either approach alone?

The “Maltalep” trial (so-called as it is funded by The Order of Malta), now running in North West Bangladesh is designed to throw light on this question. It is a randomised (but not double blind) controlled trial comparing the effect of “BCG booster alone” or “BCG booster plus SDR” in protecting close contacts of newly diagnosed leprosy cases. The Leprosy Mission Bangladesh is proud to be hosting this important trial, which is similar in methodology to the famous “COLEP” trial (which gave good evidence on effectiveness of SDR alone, compared with placebo). Since 2012, whenever a new leprosy case is diagnosed and starts MDT in the 4 districts comprising the field research unit, the patient is considered for inclusion in Maltalep, if he and his contacts are agreeable, the household will be randomised to one of the 2 arms and followed up for 2 years to see the effect. All contacts who are subjects in the trial receive BCG as soon as they have been checked for leprosy and found healthy. About 8 weeks later half receive a single dose of rifampicin. One of the interesting findings already has been the relatively large number of new leprosy cases (from amongst healthy contacts) who are diagnosed at 8-12 weeks after enrolment: we believe this to be a reflection of the immune stimulation due to BCG making previously-unapparent skin lesions become clearly visible. That is to say the subject already had leprosy infection - but in a sub-clinical form - at the time he received his BCG dose, so that even our trained leprosy staff could not detect the disease by physical examination; then giving BCG raised the level of cell mediated immunity precipitating a mild form of “reversal reaction”. A similar phenomenon is sometimes observed in leprosy-endemic countries in people with HIV who start anti-retroviral therapy (immune reconstitution inflammatory syndrome). These findings have now been published in the journal Vaccine

The team aims to include 20,000 healthy contacts (about 15 per index case) and already more than half that number is enrolled. At the same time, blood from some of the subjects (a 1 in 4 random sample) is being collected for another study (under the IDEAL consortium). These blood samples will be used to try and identify biological markers which could help in diagnosis of subclinical or overt leprosy infection, or to predict which people with very early leprosy infection are more likely to progress to actual disease.

Within the next few years there is likely to be much progress in building the evidence base which is needed for correct decisions to be made about prophylaxis. Maybe BCG booster doses for all healthy contacts are a good idea, but would selected contacts benefit even more from having SDR as well as BCG? Those who have already been exposed to leprosy by prolonged household contact with a newly diagnosed case have a higher risk of developing leprosy than the general population, but of course their extra risk falls towards the background level for that population as soon as the index case is on MDT. Occupational risk for health workers is different matter, since it involves repeated short exposures to a series of different individuals with untreated leprosy: single dose rifampicin prophylaxis is not going to be effective for this type of exposure, but it would be interesting to assess the benefit specifically amongst health workers from a booster dose of BCG!
SBL SAC

The Scientific Advisory Committee of the Stanley Browne laboratory met on 1st March 2016 at TLM Community Hospital Shahdara. The year’s progress was reviewed and the members gave valuable inputs which will improve the work even further.

Translation Workshops for “Bench to Basti”

Translation Workshops for the “Bench to Basti” project were held at Miraj, Maharashtra with the senior staff and Programme Managers of TLM Community programmes and at Bilaspur with District Leprosy Officers and NLEP staff from the Government of Chattisgarh. More details about these meetings can be found in the article by Dr. Pim Kuipers on Pg.1.

Early Detection Project Workshop

A 3 day workshop for the staff of the Early Detection Project supported by the Leprosy Research Foundation was held at TLM Hospital Chandkuri. Staff from GLRA, NLR and TLM from all five sites of the study attended and participated in the in-depth participatory sessions to prepare for interventions in the community.

Interaction with CREATE

As research is an integral part of the field project CREATE, research domain is actively involved in the research aspects of the project. Dr. MS Raju from the Research Domain, along with Dr. B Ebenso from Leeds University, UK facilitated a 3-day orientation and induction programme for the project at a workshop in Miraj, during 27th - 29th January 2016. At this orientation research possibilities through CREATE project were identified and formation of scientific research advisory committee for the project was discussed.

5-day staff capacity building workshop

Dr. MS Raju from TLM Research took part as one of the facilitators along with Mr. Kurian, in a five day training workshop organized with the objective of capacity building for the staff of the CREATE project, during March 12 - 16, 2016, at ICSA Pariyurna Training Centre, Chennai. MS Raju’s role in the workshop was Research Orientation and to facilitate identification of possible research questions by the participating members of the community action project.
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<td>Compressive ulnar nerve neuropathy resembling nerve abscess at a leprosy referral hospital in Purulia, a high endemic district in India</td>
<td>Lepr Rev (2015) 86, 292–295</td>
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