Editorial

Dear Friends,

We are back after rather a long gap. We were unable to publish the 3rd quarter issue of this Newsletter due to unavoidable reasons, and we hope all the news and articles in this issue make up for the wait.

The most talked about issue in leprosy circles recently has been around the development of WHO’s new global strategy for the next 5 years. One of the most controversial elements in this strategy is the possible recommendation of UMDT (Uniform Multi Drug Therapy) for all types of leprosy. Our main article in this issue is regarding the merits and demerits of implementing UMDT in national leprosy programmes. Please do send us your comments and response to this article, as there seems to be wide range of opinions.

The Leprosy Mission Trust India conducted a Symposium on Emerging Issues in Leprosy, on 3rd November. This was attended by leprosy experts from different disciplines and organisations, including representatives from the Government of India. This initiative was greatly appreciated by those who attended and resulted in a list of recommendations to be made to the National Leprosy Eradication Programme. One of these recommendations happens to be ‘not to implement UMDT’ in NLEP.

Apart from this there are short articles about the ENLIST group, the experiences of a medical student visiting TLM Trust India and news of our activities and abstracts of papers published by TLMTI staff.

As we come to the close of yet another year, we thank you for your support and encouragement and wish you a Blessed Christmas and Happy New Year.

With warm wishes,

Annamma S. John
Editor & Head (Research & Training)
The programme ended with a panel discussion during which the panellists presented their recommendations, based on the research papers and the discussions held during the day. Given below are some of the recommendations that were made:

1. Increase attention to training of young medical professionals so that they can diagnose leprosy and early nerve damage, and treat them.
2. Creating and maintaining leprosy expertise by Empowerment of PHC staff, health care workers and all medical care professionals for suspecting and bringing in early cases of leprosy for diagnosis.
3. Empowerment of the community in facilitating accessibility of treatment and reduction of stigma.
4. Introduction of immunotherapy and immunoprophylaxis (by Leprovac inoculation) in the NLEP; especially for MB cases.
5. Reintroduction of practice of slit skin smear in the PHCs and NLEP to facilitate identification of Relapse, resistance and MB cases with no visible patches (Infiltrative).
6. Patient should not be released from treatment until MI ‘Zero’ is attained.
7. NLEP should not accept UMDT for MB patients.
8. MB leprosy patients with high BI/Mi (>4) often do not respond adequately to 12 months MDT MB Regime. Long term follow up should be done for them.
9. Detect early reaction and nerve damage for high risk group of leprosy patients with the help of bio-marker like IP-10 and if any other biomarkers are found.
10. Leprosy cases with BI 4+ or more should be kept on longer follow up while on a drug trial.
11. Focused brainstorming sessions comprising of dermatologists, immunologists, bacteriologists and other experts to discuss and develop strategies to combat Drug resistance. GOI, WHO, ILEP and ICMR should lead this.
13. Initiative need to be taken for development of second line anti leprosy treatment.
14. Have inter-sectoral and inter-ministry plans and activities for improvement of services to leprosy patients.
15. Attention to Advocacy initiatives.
16. Empower people affected by leprosy suffering from reaction to tell doctors about the subtle symptoms of reaction.

17. Improve and increase IEC campaigns, developing them in a scientific manner with communication experts.
18. Create a system to identify high risk individuals for developing leprosy.

TLMTI will submit these recommendations to Dr Anil Kumar, Deputy Director General (Leprosy), Ministry of Health and Family Welfare, Govt of India who was the chief guest of the programme.

In England (where tailors are a rare luxury) people commonly buy ready-made garments and they may be labelled small / medium / large, but are often marked as “one size fits all”. Now I do not trust this claim: maybe the tee shirt or the trousers will fit “nearly enough” for 2 out of 3 purchasers, but some people are unusually large or small or an unusual shape. For some of them the item of clothing will be tight with inadequate length of sleeve or leg, and for others it will be excessively loose, interfering with movement. Now this might sound like the introduction to an article about provision of specialised footwear…. but I want to talk about the idea of “one treatment suits all”.

The WHO recently circulated a draft of their Strategy for the next 5 years, inviting comments from organisations like TLM. Some of us were worried about certain components of the strategy. Here is one of them: “Promote use of shorter, uniform treatment regimen for all categories of leprosy (Target: Use of Uniform MDT in the programme)”. This new recommendation is not supported – in the WHO draft strategy document – either by evidence of its safety & effectiveness or by a description of the regimen.

The idea of “uniform MDT” was introduced at the International leprosy Congress in 20002 in Brazil.

What is UMDT and why should we use it?

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The idea of “uniform MDT” was introduced at the International leprosy Congress in 20002 in Brazil.
Supposedly it would be one simple regimen of multidrug therapy expected to adequately treat all leprosy cases without health workers needing to classify them into different categories. The proposed regimen is the same drugs and dosages as in standard MB MDT, but for only 6 months, or (one might say) the same regimen as standard PB MDT but with clofazimine added. Participants at the ILC were invited to participate in multicentre trials of this so-called “UMDT”, and over the next few years several centres began trials, however to date there is not much good quality evidence published in peer-reviewed journals, on which to base decisions about implementation of the “UMDT”.

What would you like to know before using it in your clinics? I suggest that, at minimum, we seek answers to these questions:

For PB patients, is the extra medicine beneficial, or might it do harm?

For MB patients, will 6m treatment be enough to bring about a bacteriological cure, as judged by incidence of relapse after 6m MDT, or as judged by the proxy outcome of “fall in BI of skin smear”?

For MB patients will the shorter course put patients at higher risk of reactions and subsequent disability?

For the last 2 questions one might want separate information for those who were initially smear positive or those who were smear negative from diagnosis.

Will abandoning the requirement for classification indirectly lead to neglect of complications (since knowing whether someone is PB or MB helps to predict his/her risk of complications so determines some aspects of care)?

So now, 13 years after the idea was publicised, can we be confident that “one treatment suits all” in respect of leprosy infection?

In TLM Bangladesh, in 2004, we set up a study observing 2 cohorts of MB patients who received either 6m or 12m of triple therapy, and have followed them up for the past 8-10 years. Very soon this study will be published as one contribution to the debate.

Let us look at the 5 questions in turn. UMDT for PB cases is likely to be effective (in overcoming infection) as it contains more antibacterial medication than the current regimen, and the extra medicine will probably not cause much toxicity/many adverse reactions (we know that daily 50mg clofazimine is well-tolerated by most MB cases). It will be more expensive but patients will not have to bear that cost. PB patients are unlikely to benefit from the clofazimine in terms of its anti-reaction effect since they are not at risk of ENL reaction. One study in South America looked at the “acceptability” of the triple drug regimen in PB cases and reported that PB patients were generally happy to take the triple therapy for 6m(1). This was important, because in fair skinned people the clofazimine discoloration of skin, typically greater on the leprosy patches, may be a social embarrassment: it might be more conspicuous than in MB cases with diffuse infiltration where the colour is evenly dispersed. One advantage of UMDT might be that the few unusual patients with high bacterial load but few skin lesions (who are at risk of being misclassified as PB if they do not have a skin smear) will receive a more adequate course of MDT.

Several studies have been published showing that there is a low relapse rate after 6m MB MDT for MB cases, but mostly these have only short follow up and true relapse (due to persisting M leprae) may occur many years after RFT. After 6 years follow up, amongst 1302 MB cases who had UMDT, there were 6 relapses in one study(2) and amongst 114 MB cases treated with UMDT in China there was 1 relapse(3,4), while follow up to maximum 6.6 years (2139 pyar) of 323 MB cases in Brazil produced 2 relapses(5). One other UMDT study resulted in 4 relapse amongst 1136 MB cases, but the time period was unclear.(6)

It is reassuring to know from some publications that positive skin smears do become negative after 6m treatment of MB leprosy ... but there are few reports and on a small number of cases. One study showed that 98.7% of smear positive cases (including 21 Highly Smear Positive) became negative by 6 years after 114 cases were given UMDT(3). Another showed that the rate of fall of BI was not significantly different between those who had had 6m or 12m MB MDT(6), even in those initially Highly Smear Positive.

One assumes that if the BI falls the risk of ENL will also decline, but there is hardly any published evidence to date on the disability outcomes of MB cases treated with shorter MDT regimens. One thing is certain, that with shorter courses of MDT a higher proportion of the reactions will occur after RFT (and hence may not be promptly and adequately treated, unless patients come regularly for continued observation).

At present, classifying cases as PB or MB serves not only to identify the MDT regimen they need but also to assess their risk of certain complications of leprosy including new nerve function impairment, or ENL reaction or iridocyclitis. At the same time it helps us to identify those cases which are at very low risk of complications and can be reassured that they have a favourable prognosis (PB cases with no nerve function impairment at diagnosis). If we do not think about classification, we will not be able to plan & give individualised care. Another use of the classification is to indicate the risk to household contacts – since it is known that household contacts of MB cases are at higher risk of contracting leprosy than similar contacts of PB cases. By the way, it is unlikely that there would be greater risk to contacts after a shorter MDT regimen, since the infectivity of leprosy cases falls so rapidly
after the first dose of rifampicin.

About 20 years ago the recommended length of a standard “fixed duration MDT” course for MB cases was reduced from 24m to 12m, without a strong evidence base(7). Fortunately, for most MB patients 12m does seem to be enough, the relapse rate up to 10 years after RFT is apparently low. But many investigators have shown that for highly smear positive cases the relapse rates are higher than for other cases (and higher after shorter courses of treatment), therefore some programmes allow all these highly smear positive cases to be given 24m MBMDT. Sadly there is still not much good quality evidence from large scale control programmes about the relative effectiveness of 12 or 24m treatment in this sub group of cases with an extremely high bacterial load(8). If UMDT is introduced widely it is essential that such studies are set up to compare outcomes of 6m with 12m (or 24m) MBMDT, in places where skin smears can be routinely and reliably done. I would also be worried about smear positive MB patients who have suffered dapsone hypersensitivity syndrome and are given only 2 drugs (rifampicin and clofazimine) - will 6m be enough treatment for these vulnerable people?

In my opinion, it is unwise at this stage to assume that “one treatment suits all” and we should be cautious about hurrying to implement a recommendation which is not supported by adequate evidence. Perhaps UMDT will soon become the standard or “minimum” treatment offered in national control programmes, at clinics staffed by generic health workers with a low level of leprosy knowledge. However, I trust that in situation like TLM clinics where higher technical standards can be maintained, we will continue to offer a more individualised approach to treatment, taking into account the patient’s skin smear results as well as the clinical presentation of leprosy. This may mean we give “more than the minimum” to those with a high bacterial load and other risk factors, but we may also want to give “less than the standard” treatment to those at low risk (eg. only 2 drugs for 6m for single lesion smear negative PB cases). A tailor-made approach! I trust that we will also be closely monitoring not only individual patients but also clinic-level outcome data in order to learn from our experiences.

References (from 6m MBMDT paper, draft 28.9.15)
management of leprosy and common dermatological conditions. Before this began, I was able to see the work that went on within the Stanley Browne Laboratory, where much important work occurs in investigating the nature of Mycobacterium leprae. I was able to see how the laboratory operated, including procedures such as Polymerase Chain Reaction and Enzyme Linked Immunosorbent Assays.

I was also able to be involved in some of the research, too, although my role was very minor. One project was to determine whether M. leprae was present in the nasal mucosae of paucibacillary patients; although I was meant to help in collecting samples in Purulia, the staff was very efficient and managed to collect the nasal swabs and record them all for me! Another project was to determine the relapse rate of leprosy in Purulia. This work involved searching through previous pathological laboratory reports of biopsies to ascertain whether patients had relapsed. This work was most interesting, as when going through the reports it appeared as if certain patterns were emerging. It was also an opportunity to learn about the pathology in relapse, resolving leprosy, and the skin in reaction. Other minor jobs included helping other researchers with the writing of their research, such as helping with the discussions and proof-checking.

I had a very edifying time in India, and one day I would like to return. Many thanks to everyone for making my stay most enjoyable.

Alasdair Menzies
Medical Elective

Events

ENLIST Workshop
TLM Purulia, is member of the ENLIST study group which is engaged in research on different aspects of ENLs. At present the group is working on development of a severity scale for ENL Reactions. A workshop was held at Purulia on 27th and 28th of July to train the staff engaged in this project. Dr. Ruth Butlin was the facilitator.

Research Methodology in Advocacy & Health Communication
This Workshop, a joint effort by Advocacy & Communication and Research & Training Domains, was held from August 25 - 28, 2015, at TLM Media Centre, NOIDA. This training was an initiative undertaken to train the key staff in research design and methodology, communicating evidence-based research, some aspects of data collection and analysis etc. The expected outcome of this training is to be able to identify and conceptualise relevant research topics in the domain of Advocacy and Communication and also to overcome the fear and mystery associated with research. 17 key staff from various TLMTI centres participated in the Workshop.

Training of TLMTI Medical Officers
The Training of the 2nd & 3rd. Batches of Medical officers was conducted in TLM Shahdara and TLM Naini. The 2nd MO course was conducted between August 11 - 19, while the 3rd was conducted between September 1 - 9. Altogether 55 doctors have been trained this year. The course curriculum was the same in all the courses and the subjects included leprosy, Disability Management, advocacy, NTDs& WASH, NLEP and Community issues. The course reflected the TLMTI’s Moto of Healing, Inclusion, Dignity as it had dealt with all the aspects of a holistic approach towards the Leprosy affected. The Facilitators comprised experts both from TLMTI and external.

Leprosy Symposium
A symposium entitled ‘Emerging Needs in Leprosy
Research in the Post Elimination Era’ was conducted by TLMTI on 3rd. November 2015. (details on pg.1-2)

**Workshop for ‘Early Detection’ project**

A Workshop was held at Media Centre NOIDA on 18th, 19th & 20th November to initiate the LRI funded project ‘A comparison of three types of targeted, community-based health education aimed at promoting early detection. Doctors and Field staff from NLR, GLRA and TLMTI participated in this workshop where Standard operating procedures for the project were developed and the staff oriented and trained.

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**ENLIST**

We all know that ENL reaction is an unpleasant complication of leprosy: it causes suffering and may lead to permanent disability. Prednisolone helps many patients with ENL reaction, high dose clofazimine may suppress chronic ENL reaction, and thalidomide is extremely useful if it is available and not contra-indicated, but there is a need for other second line drugs and steroid-sparing agents which are proven safe & effective. In order to conduct good quality trials of anti-reaction drugs we need a reliable way to measure severity of reaction: there is already a validated scale for reversal reaction (3) but nothing comparable for ENL. At any one centre there are unlikely to be enough patients to undertake the type of studies needed. For all these reasons the work of ENLIST is of vital importance and we are proud that TLM India is involved in the ENLIST projects.

“Enlist” is a group of research teams interested in the problem of ENL reaction, based at 9 leprosy centres of which 3 are TLM’s: Purulia in West Bengal, Anandaban Hospital & Mycobacterial research laboratory in Nepal, and DBLM hospital at Nilphamari in Bangladesh. The others are in Philippines, Ethiopia, Brazil, Indonesia, Mumbai, and UK (London school of tropical medicine & hygiene). Their collaboration began in 2012 (1), and so far has resulted in highly fruitful interactions through 3 workshops for face to face discussion and a number of Skype conversations, plus innumerable email communications.

The first major joint study, looking at features of ENL has been written up by Dr Steve Walker and that paper is already submitted to a journal. A second multicentre study on Quality of life in people affected by ENL is in analysis stage. A third project (for which the Leprosy Research Initiative has given funding) is the development of a scale to measure severity of ENL, which is now practically ready to be implemented. The scale will include items reflecting the patients’ opinion/experience as well as those features which seem important to clinicians.

The next project is a more ambitious one - to run two randomised controlled clinical trials, assessing the effect of methotrexate in either acute/chronic ENL reaction (and using the newly-validated severity scale for an outcome measure). This is also expected to be funded by Leprosy Research Initiative. Alongside the RCTs, there will be an opportunity to build up a biobank of material which we hope will later provide useful information on genetic factors related to severity of reaction, and on immunological processes involved in reaction.

Alongside these collaborative studies some centres have completed their own related studies – most notably the one on economic impact of ENL reaction done at Purulia (2).

Once again TLM is at the forefront of leprosy research, seeking answers to the questions which matter most to leprosy-affected people!

**References**


**Dr. C R Butlin**
Abstracts

Changes in plantar load distribution and gait pattern following foot drop correction in leprosy affected patients

Mrinmoy Karmakar, Jerry Joshua & Nidhu Mahato

This study was done to compare the changes in plantar load (weight distribution) and gait patterns before and after tibialis posterior transfer surgery in people affected by leprosy. Changes in gait patterns were observed and proportionate changes in plantar load were quantified using data captured by a baropodometer. All the eight patients who underwent tibialis posterior transfer surgery in 2013 in our hospital were included in the study. In addition to the regular pre-operative and post-operative assessments, the patients also underwent baropodometric evaluation. There was a significant change in plantar load at the heel, lateral border and forefoot. Using the foot pressure scan, it was noted that the progression of the centre of mass (displayed graphically as ‘the gait line’) was also affected by the altered pattern of weight distribution. This study reiterates the importance of tibialis posterior transfer because: it restores the normal gait pattern of 1, 2, 3 (where 1 is heel strike, 2 is mid foot contact and 3 is forefoot contact) and provides a more uniform distribution of planter load.

Emergence of primary drug resistance to rifampicin in Mycobacterium leprae strains from leprosy patients in India.

Clin Microbiol Infect. 2015 Aug 24

To overcome the challenge of containing the disease and to sustain the ongoing declining trend of leprosy in endemic countries, it is essential to monitor drug sensitivity patterns in the present settings. The Leprosy Mission (TLM) Trust India is one of the sentinel centres of the WHO for surveillance of drug resistance in leprosy. The WHO sentinel surveillance was undertaken to identify leprosy patients who already completed an MDT regimen and had relapsed, and did not show any reduction in the activity of their lesions and bacteriological indices (BIs), in spite of re-introduction of MDT. The cases were classified as multibacillary and paucibacillary, according to WHO guidelines. Along with these cases, we enrolled some new cases with high BIs who had not been treated with any MDT before recruitment, to detect primary drug resistance. Primary drug resistance refers to patients who have never been treated for leprosy with MDT. A total of 215 slit-skin scrapings from relapsed leprosy patients and new patients were obtained between 2009 and 2014. Among these 215 cases, there were 184 cases of relapse, 16 new cases, and five defaulters. Among the 16 new cases, we observed mutations at already reported codon positions (424, 425, 437, and 438) and at a new codon position (411) in rpoB in three patients. Among these 16 new cases, seven showed primary resistance to rifampicin. Of these seven cases, three cases showed a mutation at codon 411 (Ala/Val) that has not been reported previously.


Erythema nodosum leprosum (ENL) is a severe multisystem immune mediated complication of borderline lepromatous leprosy and lepromatous leprosy. ENL is associated with skin lesions, neuritis, arthritis, dactylitis, eye inflammation, osteitis, orchitis, lymphadenitis and nephritis. The treatment of ENL requires immunosuppression, which is often required for prolonged periods of time and may lead to serious adverse effects. ENL and its treatment is associated with increased mortality and economic hardship. Improved, evidence-based treatments for ENL are needed; however, defining the severity of ENL and outcome measures for treatment studies is difficult because of the multiple organ systems involved. A cross-sectional study was performed, by the members of the Erythema Nodosum Leprosum International Study (ENLIST) Group, of patients with ENL attending seven leprosy referral centres in Brazil, Ethiopia, India, Nepal, the Philippines and the United Kingdom. We systematically documented the clinical features and type of ENL, its severity and the drugs used to treat it. Patients with chronic ENL were more likely to be assessed as having severe ENL. Pain, the most frequent symptom, assessed using a semi-quantitative scale was significantly worse in individuals with “severe” ENL. Our findings will determine the items to be included in a severity scale of ENL which we are developing and validating. The study also provides data on the clinical features of ENL, which can be incorporated into a definition of ENL and used for outcome measures in treatment studies.
MAY
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OF
Christmas
BE WITH YOU
NOW AND THROUGHOUT
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NEW YEAR
From all in the
RESEARCH & TRAINING DOMAIN

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