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Report

17th International Leprosy Congress, Hyderabad
Reports of Pre-Congress Workshops held on January 29th-30th, 2008

P.S. These reports are being printed as prepared by Rapporteurs and Chairpersons, without any editorial corrections.

Pre-Congress Workshop I

"New Diagnostics and Molecular Epidemiology"

(Organizers : Drs John Spencer, Thomas Gillis and Vissa Varalakshmi)

Morning Session: New Diagnostics (morning session, 0900-1300) Organizer: Dr. John S. Spencer, Colorado State University, USA

Diagnostics moderators: Linda Oskam, KIT/Annemiek Geluk, lUMC/Maicoim Duthie, IDRI

Rapporteur: Diagnostics: Professor Warwick Britton, Head, Mycobacterial Research Group, Centenary Institute, Australia

Afternoon Session: Molecular Epidemiology (afternoon session, 1400-1700) Organizer: Dr. Vissa Varalakshmi, Colorado State University, USA

Molecular Epidemiology moderators: Drs. Thomas Gillis, NHDP ; Vissa Varalakshmi, CSU

Morning Session: New Diagnostics

Dr. Annemiek Geluk: "Development of novel T cell assays for detection of *M. leprae* infection."

Unique proteins and peptides diagnostics are being concurrently evaluated for specificity and sensitivity with the additional constraints of being intuitive to utilize for clinicians without the additional burden(s) of specific laboratory equipment for either procedure or interpretation. To that end, investigation is ongoing for a test in a 'lateral flow type' platform which can be used with whole blood (WBA) as opposed to peripheral mononuclear cells (PBMCs). The difficulty with the WBA is the loss of some specificity and the dilution of the cytokine ratios of responsivity. Recombinant ML2283 and other *M. leprae*-specific proteins are being investigated as a means to differentiate immune responses for healthy household contacts (HHC), which typically do not show a response for PGL-1. Initial results are promising, but require further study and resolution to ensure increased reliability of immune/cytokine profiling. As a further adjunct diagnostic, a new assay using U-Cytech (UPT converting phosphor technology) was added to the WBA. In this assay, light of a lower energy is converted to light of a higher energy. UPT reporter particles then absorb infrared light and emit a detectable signal.

The combination of the U-Cytech Ab of IFN-gamma ELISA were applied in a lateral flow 'immuno-sandwich' to combine both technologies in a field friendly format, called the UPT-LF for IFN-gamma detection. The measurement is a ratio of control versus outcome, each strip is then its own control. UPT has a portable reader which can do either one flow strip at a time or multiple strips.

Research is ongoing to identify proteins or other target antigens to improve sensitivity and specificity, particularly for IT/BT individuals.

Dr. Linda Oskam: "New and improved opportunities for a serological kit and use of serology in leprosy control to aid classification and predict nerve function impairment."

The ML Flow test was evaluated as an additional, serological, tool for the classification of new leprosy patients in Brazil, Nepal and Nigeria. 2632 leprosy patients were classified using three methods: (1) counting the number of skin lesions, (2) slit skin smear examination, (3) serology using the ML Flow test. In Brazil and Nepal about 1/3 of the patients were MB against 1/5 in Nepal. Seropositivity was 63% in Nigeria, 51% in Brazil and 36% in Nepal. ML Flow test results and smears were negative in the vast majority of PB patients and in 16% of Brazilian and 38% of Nepali MB patients. Testing all PB patients with the ML Flow test to prevent under-treatment would increase the MB group by 18%, 11 % and 46% for Brazil, Nepal and Nigeria. Using the ML Flow test as the sole criterion for classification would result in an increase of 11 % and 44% of patients requiring MB treatment in Brazil and Nigeria and a decrease of 4% for Nepal. The ML Flow test could be used to strengthen classification, reduce the risk of under-treatment and minimize the need for slit skin smears.

Anti-PGL-1 IgM seropositivity reflects the systemic bacterial load of leprosy patients. It aids the diagnosis and classification of leprosy patients and can be used to predict nerve function impairment (NFl). Despite this, serology is still not used in routine practice, possibly due to perceived lack of applicability and costs. Here we provide strong evidence that serology is valuable for and can be used in routine leprosy control. 1037 new leprosy patients were included in a prospective cohort. The relation between clinical and demographical variables and seropositivity was calculated and the test potential to predict NFl was determined using survival analysis. The number and extent of clinical signs as well as sex, age, disability grade, bacterial index and classification all correlated with seropositivity. The size of skin lesions was positively correlated with seropositivity. No difference in levels of seropositivity among patients with one or two skin lesions was observed, nor were there different levels among patients with or without satellite lesions. A NFl prediction rule, was proposed using classification and serology results, which could predict 80% of all NFl events in the cohort.

Dr. Sang-Nae Cho: "Enzyme immunoassays for PGL-1 antigen and antibodies."

Dr. Cho independently described his independently developed lateral flow kit and the pending comparison with the work developed by Drs. Oskam and Buhrer. He described other forms of ELISA based on 35kD, 36kD, and 45kD protein antigens. In particular the combination of 45kD and PGL-1 based serology adds considerably to the power of the latter. In particular, he described finger-prick PGL-1 based serological screening of populations from endemic regions throughout Vietnam as the basis for the subsequent chemoprophylactic intervention.

Dr. Om Parkash: "Serological detection of leprosy: Recent developments at JALMA, India our laboratory."

Described independent serological studies on the use of the 45kD serine rich protein, further supporting the added value of this form of serology.

Dr.Yumi Maeda: "Recent findings of the use of the MMP-II protein as a potential diagnostic for leprosy detection using serology."

The major membrane protein II (MMP II; 28kD bacterioferritin) was generated as a fusion protein, affinity purified and applied as an additional serological tool in the context of conventional ELISA and compared with the PGL-1 based particle agglutination test. Evidence was presented that this combination provides an additional means for the detection of leprosy.

Dr. Malcom Dutihie: "Evaluation of the LlD-1 fusion protein for the serological detection of *M. leprae*."

The aim of the work is to provide an early case detection/diagnosis serologically based test which would lend itself to widespread, early and intuitive application. The crux of the current work is the utilization of select antigens from the known repertoire of recombinant antigens in stock. Serological expression cloning using select engineered combinations of these protein based antigens (fusion proteins containing pieces of several proteins) are under investigation. The work presented focused on the utilization of L1D-1, a synthetic combination of ML0405 and ML2331. L1D-1 utilized in combination with PGL-1 has generated intriguing results worthy of further investigation and refinement. This line of research holds promise for leprosy diagnosis.

Dr. John Spencer: "Use of Western blot, ELISA and protein microarrays to define disease-state-specific antigenic profiles in leprosy."

The current serodiagnostic test for individuals with leprosy is based on antibody responses to the *M. leprae*-specific phenolic glycolipid-1 (PGL-1). To further understand the relationship of antibody responses to disease state, the reactivity patterns of 50 lepromatous and 20 tuberculoid sera to PGL-1, lipoarabinomannan (LAM) and six recombinant *M. leprae* proteins, was examined. The response to Ag85 was consistently high in both patient groups, while responses to CFP-10 and GroES showed the most variability, from strongly positive to completely negative. The tuberculoid patient sera showed overall lower responses to all of the recombinant proteins, particularly in the case of GroES, where none in this group showed any reactivity to this protein. Only 25% of these same patients showed a weak response to CFP-10, while 76% of lepromatous patients showed a positive reaction to this protein. This analysis has given a clearer understanding of some of the differences in the responses, both between individuals at opposite ends of the disease spectrum, as well as illustrating the heterogeneity of antibody responses towards protein, carbohydrate, and glycolipid antigens within a group. Attempts will be made in future to determine if some of these response patterns can be correlated with a particular disease state or outcome.

Dr. Juan Periche Fernandez: "Difficulties in leprosy diagnosis."

Dr. Juan Periche presented the paramount need for laboratory based testing which can be readily applied in the field to assist the clinician with the accurate diagnosis of leprosy. Clinical diagnosis based solely on physical examination is often difficult. Data was presented on the importance of active and passive leprosy case discovery. Utilization of active leprosy case discovery through the interview process of healthy household contacts, in combination with experiehced clinical examination, yielded the greatest benefit and was the most efficacious for cumulative resource utilization. Definitive serological/cell

immunity-based tests would add greatly to this effort

Major Recommendations:

- PGL-1 based serology, particularly in the kit format, continues to playa greater role in leprosy control in the following manner:

- as a confirmatory marker
- a predictor of disease outcome
- an indication of nerve damage and exacerbation
- as a tool for pre-clinical intervention.

- Protein based serology in the microarray format adds to diagnostic resolution and may aid in early clinical detection, once reduced to a 'field friendly format.'

- Assays based on cellular immune responses, and the facile detection of gamma interferon; may assist in pre-clinical detection allowing for early diagnosis and appropriate treatment.

Afternoon session: "Molecular Epidemiology."

The afternoon portion of the Pre-Congress Workshop was devoted to topics in the general area of the molecular biology of *M. leprae*, organized and chaired by Drs. Vissa Varalakshmi and Thomas Gillis. Discussions centered on two major themes, **Diagnostic and Environmental and Clinical.** The former focused firstly and briefly on the ***Diagnostic Potential of PCR in Comparison to Immunological Approaches***. There were three presentations, by Drs. Xiaomen Weng, Benjawan Phetsuksiri and Malcolm Duthie. Drs. Weng and Duthie described experiences with protein-based antigens, particularly the chimeric fusion protein, L1D-1, in serological and cellular immune formats with different populations, whereas Dr. Phetsuksiri described her applications of a very sensitive version of RT-PCR, capable of detecting as few as 3-4 bacilli. However, the conclusion was that PCR, even in its most sensitive format, is most suitable for purposes of confirmatory diagnosis in light of reliance on biopsy specimens, and for the continuing examination of the relationship between nasal carriage and true infection. Discussions on the topic of ***M. leprae in the Environment*** were wide-ranging led by brief presentations by Drs. Ramanesh, Amare, Izumi, Rupendra, Gillis and Jadhav. Beyond the well-documented presence of *M. leprae* in wild armadillos in the south of the USA, there were now reports, as yet not adequately documented, of its presence in Brazilian and Columbian armadillos, besides in water and soils. However, most of these reportings were from areas of high endemicity suggestive of human origin. Questions of whether merely DNA rather than viable *M. leprae* was being observed, and significance in terms of human transmission, were raised. The consensus was that no meaningful hypothesis could be posed at this time, but rather continue to observe and report. The second major theme of this molecular biology portion of the Pre-Congress Workshop, namely **Clinical** aspects, was discussed firstly under the sub-heading of ***Molecular Markers***. Dr. Vissa summarized the diverse features of the present well known -20 VNTRs in terms of stability and applicability to different epidemiological questions (global vs. community vs. household transmission), different geographical settings, etc., indicating that the goal was to arrive at a set of markers of different properties to address different questions. She emphasized that the search for suitable diverse markers will continue, particularly now with the availability of a second *M. leprae* sequenced genome. Dr. Gillis, laid out some statistical rules for the analysis of data to arrive at meaningful conclusions, indicating that -20-25 VNTRs with a boot-strap value of >80%

will be needed. Dr. Cole produced data on the lack of robustness of some of the markers used to date to truly address the questions posed, particularly some AT-rich micro- and mini-VNTR satellites. He emphasized the power of SNPs to address the historical origins of leprosy; however, these were too stable to address more immediate transmission questions. Dr. Vishwa Mohan Katoch described his experience of the application of VNTR-based molecular epidemiology in high transmission areas of Northern India, areas where evidence of *M. leprae* in the soil was well established. At this stage, the emphasis was on collection of samples, standardization of techniques and selection and optimization of markers. Embedded in this very productive session were discussions on the ***Practicalities of Molecular Epidemiological Studies***. Dr. Belagon contributed to this discussion with her experience in Cebu. The need for properly documented cohorts, training, SOPs, suitable equipment and materials, databases, planning such as that conducted by the IDEAL Consortium, were all emphasized by Dr. Vissa and amplified by the attendees.

The final topic of the afternoon session was ***Drug Resistance***. This was led by Dr. Matsuoka and his studies in several global settings (much of it published). The need for well-planned surveys led by the Leprosy Control Programme at WHO, were emphasized. The recommendations of an earlier WHO workshop at JALMA were seconded in that the collection of data on molecular evidence of RIF and Dapsone resistance should continue with haste. The question of the need and availability of mouse footpad colonies was discussed. There is no doubt that 1-2 well run, busy facilities are required and several of those in existence do not meet minimal specifications. WHO and the community should consider this issue. This topic recurred often throughout the various segments of the Congress, at Guest Lectures, Plenary Sessions, Multiple Free Paper Sessions, Posters.

Pre-Congress Workshop I continued the following morning of January 30th with a free ranging, well attended vigorous discussion on the topics of the previous day. This was a very productive, timely and successful Workshop.

The conclusions were:

- PCR is now an extremely sensitive and specific tool for diagnostic confirmation; it is not a useful diagnostic tool.
- *M. leprae* in the environment (soil, water) probably arises from human shedding; role in leprosy transmission is not known; the acquisition of data should continue
- Molecular Markers: there is consensus that certain markers, particularly AT-rich, are devoid of sufficient robustness to answer pressing epidemiological and transmission questions. Others do have potential, supported by published work; the search should continue governed by statistical 'bootstrapping' rules; there is need for input from the corresponding research communities in other infectious diseases viz. TB.
- Practicalities: The need for properly documented cohorts, training, SOPs, suitable equipment and materials, databases, cooperation planning such as that conducted by the IDEAL Consortium, was agreed. The need for shared databases, both clinical and research, was emphasized; the imposition of GPS technology in certain epidemiological settings was emphasized; the need for the

imposition of classical, population-type epidemiology was emphasized.

- Drug resistance: focus should be on RIF resistance and it can be combined with strain typing; the issue of how genetic evidence for RIF and/or Dapsone resistance might affect chemotherapy regimens should be addressed by control programs; the implementation of new simple technology such as the dot-blot hybdrization protocol was emphasized; the need for 1-2 well run, reliable mouse foot-pad colonies was emphasized; the question of the need/sustainability of subpar facilities should be addressed by funding agencies/ administrators; there are no other alternatives to MFP on the horizon.

Pre-Congress Workshop II

"Stigma, Identity and Human Rights"

(Chairpersons : Anwel Law and PK Gopal)
(Rapporteurs : Nevis Mary and Doug Soutar)

Anwei Law introduced the workshop and outlined the plan of how discussions would be taken forward. She welcomed the fact that there were participants from many different countries all of whom brought their own differing perspectives and experience. It was stressed that it had been important to include the word identity in the title of the workshop as this represented the bridge between stigma and human rights.

Quotes from previous conferences had provided inspiration in thinking about this congress.

"To get rid of the stigma, we have to have self-confidence first." –Wang Cheng Li

"We used to say that if society changes we will change. We should discard this belief and say that if we ourselves change, then society will change." –Miyoji Morimoto

"Human rights begin within us so we will start by calling each other by our own names." –IDEA Mozambique

"We believe that if a person feels dignity, they will not allow anyone to take away their human rights."–IDEA Latin American Network

In addition to the question of where the concept of personal identify figures in human rights, it would also be important for the workshop to look at these issues in the context of fund-raising.

A short presentation was given by Gracicla Benitez from Paraguay describing her experience of Hansen's disease and how she felt in the period following her diagnosis. She went on to describe how her involvement with IDEA had represented a complete change in her life bringing her out from despair and into contact with new friends and relations. Although she still felt fear in being rejected by people, she was now committed to overcoming this hurdle.

Dr Gopal in his introduction noted that the topics were not new but had been discussed over decades. Today we had many people who were still experiencing stigma and prejudice and the question was whether we could move forward in a new direction.

Anwei explained the rationale for the division of the workshop into five smaller discussion groups to share experiences and reflect on certain key areas within the workshop topic.

The groups met over the rest of the morning and the first afternoon session. At the end of these group sessions the workshop had a brief presentation from Mr. Manohar More who described his experiences of both leprosy and HIV.

For the last session of the afternoon the five groups fed back summaries of key points and reflections from their discussions. These points, observations and some recommendations are outlined here in brief.

Group 1

This group consisted only of women and focused on their particular experience.

Participants shared experiences and it was agreed they represented women who had the courage to overcome the judgement of society. This confirmed the need for empowerment, self esteem and dignity.

Importance of creating awareness. Despite all the campaigns and improved communications, incorrect ideas about the disease and its causes still exist; traditional beliefs still persist.

Some medical staff and paramedicals are also still misinformed and these views influence their interaction with and treatment of patients.

The above confirms the need and importance of ongoing education, awareness raising, and changing of attitudes.

Legal issues need to be addressed and negative laws changed.

There is a need for a change in terminology. Although there had been a positive shift from 'patient' to 'person affected by leprosy' there was perhaps a need to review this terminology once again.

Media can play a very important role but it was recognized that over time media loses interest and ongoing efforts were required to keep leprosy issues in the forefront.

Earlier practice of isolation had contributed to stigma and the challenges faced now included making transition from 'colonies' to integrated communities.

Gender – In general the impact of leprosy and disability is greater for women than men.

The importance (but lack) of family support groups was noted similar to those for example for cancer.

For women old age is especially difficult as in this period they require more care and are more dependent especially if disabled.

All these confirm the importance of early diagnosis in order to reduce and disabilities stigma.

Group 2

This group looked in particular at the rights of the older generation and where their identity was the bridge between stigma and human rights.

The biggest issue for many was the experience of being sent away, being identified only by the disease, having to change their names and not being allowed to have children.

With increased information, stigma was gradually declining and examples of these changes were given. For example a lot was being done now by people affected by leprosy in reaching out to the wider community and children in particular. The older generation were a valuable resource but very little had been written by affected persons themselves. Leprosy museums were being created in more places in order to record and document their history and to help reflect on the changes in the attitudes of society towards them.

The closure of colonies, leprosaria, villages was an issue as urban expansion swallowed them up and there was little choice but to merge. In some cases the value

of land has increased and speculators have forced evictions. The issue of moving people to new 'hospitals' was noted giving Latvia as recent example.

In some countries like Thailand and China people have responded to these threats and real situation through demonstrations and lobbying and have had some success but information and participation is the key to enabling people to consider relocation. Forced isolation in the past has meant that relations within the segregated community have been very strong and in pursuing any relocation the concept of prior informed consent is vital to be upheld. It was recommended that IDEA should advocate strongly for this.

Group 3

Participants from 7 countries shared their experiences in this group. Their focus was primarily on the situation of leprosy colonies. Based on the discussions this group made a number of recommendations :

1a. To strengthen the identity of colonies by having them recognized as the same as other communities through a process of 'Reverse Integration'.

b. To enable the colonies to contribute to the whole community.

2. To seek more NGO support in areas such as CBR programmes, infrastructure, house building, etc as this support was felt to be more reliable and sustainable.

3. To seek government support through protection of rights by law.

Group 4

This group focused on legal issues and aspects.

Again 7 countries were represented in the discussion. The situation reported from India and Nepal appeared to be much worse than in Brazil and the other countries. One difficulty however was in measuring the number of people who are legally handicapped by outdated discriminatory laws. Key areas where such laws remained included :

Marriage and divorce (citing leprosy as justified grounds for divorce).

Inheritance laws (barring people from inheriting land and wealth).

Transport laws e.g. requiring people to have non infectivlty certificates or 'non visible' leprosy in order to travel.

Refusal of admissions to schools or general hospitals.

Employment and refusal to recruit if disclosing information of past leprosy.

In Brazil only two areas were noted that of insisting prisoners with leprosy were referred to colonies rather than prisons and discriminatory recruitment practices. In Nigeria and Ghana participants reported that IDEA had made an impact and that there were no discriminatory acts or laws in force.

It was recommended that negative laws should be deleted and that a strong lobby should be made to repeal certain laws. Moves had been made in the Indian parliament but a judgement was slow in coming and was still being awaited.

Group 5

Noerine Kaleba's participation in this group allowed for comparisons to be drawn between the experience of leprosy and HIV/AIDS. The experiences shared, both the despair and the fortitude highlighted that a lot of similarities existed in regard to stigma and discrimination. But one key difference was that leprosy is curable while AIDS is not.

A lot of the discussion in this group focused on language and terminology and whether there was a difference between stigma and discrimination. Stigma is often

perceived as an attribute of the person affected while discrimination better expresses the process of what society does to people and how it penalizes their difference. A strong plea was made to get people within the leprosy field to avoid the use of the term 'deformity'. Getting away from negative language will be important but how to continue this process ? How to help people feel better about themselves and how to correct language were important questions to continue addressing.

The family is often the first source of stigma and discrimination and it was important that both family and friends were involved in helping to overcome stigma through the creation and conservation of support systems.

Images as well as language are critical. There are still too many negative stereotypical images being used and it was recognized that this was a problem to be tackled also in the context of their use in fundraising. One question raised was whether leprosy organizations would be able to raise funds if there was no stigma and discrimination. It was stressed that images must help to reveal the identity of the person not the disease but how to do this needed more discussion.

One participant felt it was important to try and turn instances of discrimination into an opportunity to tackle ignorance and fear. Others stressed the importance of sharing experiences with others who suffer from discrimination either because of other disabilities or societal attitudes. In discussing how to change attitudes it was stressed that it was also important to consider learning from societies which didn't discriminate against people affected by leprosy.

Christiano Torres from Brazil made a plea for continuing dialogue, liberty and quality of life and to discuss what is best for every single person.

Day 2 of Workshop

Doug Soutar reported back on the key points, reflections and recommendations from the previous day (see below). The focus had been very much on seeing identity as the bridge between stigma/discrimination and human rights.

Key Issues, reflections and recommendations from the five breakout groups :

- Awareness, education, information - vital for changing attitudes
- Legal Issues urgently need to be addressed
- Language, terminology and images need continuing serious reflection
- Gender is a cross-cutting issue
- Older Generation have specific needs but are also a resource
- The places where people live – lobby for approaches based on prior informed consent
- Reverse integration can be important enabling colonies to contribute to the whole community
- Enabling support systems among family and friends is essential
- Sharing experiences and activism with others who also experience stigma and discrimination is also a priority.
- Continuing dialogue
- Aim for quality of life for ALL.

Anwei Law requested that the workshop devote some time to addressing the question of how the discussion can be translated into fundraising approaches based on justice rather than pity.

David Hall of TLM NZ indicated the need to try and focus on human rights issues and reflected on their experience of giving this focus in a fundraising letter to supporters. The positive result had indicated that there is a constituency that is willing to respond to a human right appeal.

Sunil Deepak of AIFO noted the difficulties in bring the two issues of fundraising and human rights together. Leprosy is a consequence of poverty and you have to treat all the causes. Therefore they put a lot of efforts into Human rights, CBR and promotion of empowerment.

It was felt to be important to discuss with fundraising colleagues who are still focused on pity and the use of negative images. Human Rights need to be talked about in practical and conerete terms. And this remained a big challenge.

Noerine Kaleeba noted the similarities between HIV and leprosy related stigma and stressed that the issue of identity was vital. It was important to give a human face – a positive affirmative identity to leprosy. Both leprosy and HIV have human faces. In fundraising we are dealing with people's emotions. Living with AIDS had become an acceptable slogan so why not "living with leprosy". Interaction with people affected by leprosy was vital and their participation in the whole process was important. She stressed that this had to be 'meaningful' involvement. Her maxim was that if you do a good job then this itself will raise money. No good job escapes the attention of people with good intentions.

There followed a series of presentations of the experiences of people form a number of countries including Japan, China, Ghana, Sudan, India and Taiwan. Some of these focused particularly on how they had built upon and used their experiences of leprosy and discrimination to promote and foster support and funding. The diversity and breadth of the experience shared was highlighted by the fact that this workshop had seen the participation of people from some 17 countries and contributions had been made in at least 8 different languages.

Pre-Congress Workshop III

"Reactions and Neuritis"

Clinical field experience indicates that
Reactions and Neuritis remain major issues in leprosy

(Chairpersons : Anwel Law and PK Gopal)
(Rapporteurs : Nevis Mary and Doug Soutar)

ENL

A pre-print of a paper in press by Indira Kawahita and Diana Lockwood was distributed. Presentations on pathology, immunology and gene profiling were discussed. The requirement for PMNs and vasculitis as diagnostic criteria as a criterion of ENL were discussed, noting that in a series from India, only 44% of biopsies of clinical ENL showed vasculitis. The issue of timing of the biopsy was discussed. with particular reference to the use of PMNs as a criterion for diagnosis since their appearance in tissue lesions appears to be transient. and there was consensus that a re-evaluation and standardization of pathologic critera for ENL

is advisable. The experience of ENL developing after experimental therapy with intracutaneous rIFN- was noted. and there was a discussion of the lack of understanding of mechanisms that trigger ENL. Some data from the Philippines indicates that the incidence of ENL is much higher in patients who received one year of MDT compared to those who received two years of MDT. Microchip analysis of mRNA from 13 biopsies from patients with ENL and controls, including 2 pairs of specimens, has demonstrated a large number of genes up- or down-regulated. Many of the upregulated genes are notably associated with vascular and angiogenic factors or adhesion molecule expression. This is particularly interesting in view of the suggested role of thalidomide in modulating angiogenesis. It was noted that this technology has its own challenges regarding data analysis. and that while some may regard such studies as 'fishing expeditions', others see them as voyages of discovery. In addition to indications that ENL may be an immune complex phenomenon. the potential role of CMI in ENL was discussed, noting that for both theories the evidence remains interesting but not conclusive. Presentations on clinical aspects and risk factors, detection and management in the field management in specialist centres and research needs were discussed. Regarding clinical aspects, it was emphasized that:

- Clarification is needed regarding the frequency of the different features in patients developing ENL who have received MDT.
- Prednisolone and thalidomide are effective but may have different mechanisms of action, the former mainly suppressing inflammation while thalidomide may act on underlying mechanisms.
- Well designed clinical trials are required but difficult due to relapsing nature and numbers needed.
- Standardized and validated outcome measures and severity assessments are essential in assessing therapeutic interventions.

The need was emphasized for development of laboratory tests to assist in assessment of severity and resolution of ENL. The experience of using inhibitor of TNF- infliximab, in the treatment of two patients with ENL was discussed. noting that it was highly effective but one patient relapsed and required thalidomide treatment to prevent recurrence. There is a theoretical risk that patients treated with infliximab may be at risk of relapse of their leprosy, since inflilximab has been associated with the development of clinical leprosy in leprosy endemic areas. In the field, ENL may be divided into three categories mild (single episode ENL), moderate or acute recurrent (multiple episodes of ENL for < 2 yr), and severe or chronic (continuous immunosuppression required). There is a need for good trial data on the management of mild ENL although clofazimine is widely used. The general opinion was that clofazimine in higher doses helpful in moderate ENL. The importance of recognizing iritis and other generalized involvement was discussed, as well as the need to emphasize to health workers the varied nature of ENL. Concern was expressed that ENL and its complications are less well recognized in 'integrated' health settings, where it might be judged as unimportant when health workers were unduly concerned about the overall collection of numbers of cases on treatment or released from treatment, etc. As summarized, some of the major challenges in the field are:

- Training and logistics: awareness of ENL and timely referral of cases;
- Recognition of nerve damage and iritis
- Supply of drugs - loose clofazimine and steroids are not always readily available.

TYPE I REACTIONS

The pathology and T1R and a study of correlations between pathologists in the histopathological diagnosis of T1R were presented. Data were reviewed concerning studies of histological features seen in standard H/E-stained sections, as well as studies using antibodies to evaluate the changes in HLA-DR expression, neuropeptides, and other markers, noting that none of these has, to this point, provided definitive markers for the diagnosis of T1R. An international double-blind study of the histopathological diagnosis of T1R by highly experienced pathologists demonstrated that edema, the presence of giant cells and the size of giant cells were all recognized as important features, but that other features were interpreted more selectively by individual pathologists. Overall, only 50% of reactions were clearly diagnosed histologically. The discussion highlighted the need for standardization and validation of diagnostic histopathological criteria for T1R, research to understand the triggering mechanisms of T1R, and the need for criteria to distinguish between relapse and reactions involving nerves. It was noted that triggering mechanisms may involve factors 'outside of' the immune system itself, such as neuroendocrine influences.

Presentations regarding animal models and in vitro models for nerve injury were discussed. The armadillo offers the first good animal model of neuritis in leprosy, with the opportunity to follow functional parameters such as nerve conduction together with morphologic and molecular analyses of nerve trunks at different times during the course of infection. Sequencing of the armadillo genome has begun to provide the molecular tools needed to study this model in-depth; such studies are now underway. Discussion noted that it is still necessary to delineate the limitations of this model of neuritis as compared to leprosy neuropathy in man. Hope was expressed that new studies of the armadillo model might generate an animal model for reactions, as well. Technical advances now enable gene expression analysis using microarrays to explore the changes induced in primary human Schwann cells *in vitro* after infection with *M. leprae*. Some of these experiments have been done, over 200 genes show significant up- or down-regulation 24 hr after infection, but analysis of the large database from this experiment has only begun. Studies of the role of Schwann cells in promoting chemotaxis of *M.leprae*-infected and un infected monocytes is also of interest. It was emphasized that such studies *in vitro* should be done at cooler temperatures than usual (Le., 33°C) to examine the effects of live *M. leprae*, with dies rapidly at 37°C.

Clinical aspects and risk factors for T1R and neuritis, the evidence base for therapeutic interventions, detection of T1 R in the field, and detection in specialist centers were discussed. Studies have now demonstrated that the major risk factors for nerve function impairment are 1) MB leprosy and 2) NFI before the patient is diagnosed. From these studies, it is evident that approximately 1/3 of MB patients will be affected by NFI under current circumstances of diagnosis and treatment. Evidence suggests that the best predictor of T1R is prior T1R. An evidence-based review of the treatment of reactions noted that long-term

administration of corticosteroids is problematic due to many side-effects, and opened the question as to whether there is an optimal corticosteroid regimen. Many participants felt that there is not yet convincing evidence of an optimal regimen, and opted for individually tailored treatment. The discussion highlighted the need for randomized controlled trials of corticosteroid regimens alone and in combination with other agents. Preliminary evidence from 13 countries with widely differing characteristics, concerning the detection of T1R and neuritis in the field, suggests that knowledge of T1R and skills to detect T1R are not good in most field sites, largely due to poor supervision and emphasis in training programs on detection of leprosy without regard for detection of reactions. Prevention of disability appears to be discounted as an important issue in many countries, and often health workers are alerted only if pain is an issue. Discussion highlighted the need for a simple, easy to use assessment tool for health workers, and for a clear mechanism of referral to specialized centers when indicated. New studies on the use of ultrasonography using color Doppler technology for the evaluation of neuritis was discussed, and the participants agreed that it was important to extend clinical research into such advanced technology areas in specialty centers, in addition to continuing field research using simpler techniques.

Type 1 Reactions and Neuritis

Management of T1R and neuritis in the field continues to present many challenges. Reactions and neuritis remain major burdens for leprosy control programs, and assessment methods at present are too subjective and are prone to misinterpretation. Some areas noted a decline in PB patients overall but no decline the MB patients with Reactions. The need continues to develop good programs for management of these complications in integrated settings, and the use of newly available technology such as mobile phones to facilitate communication between field clinics and referral centers. As the total number of known patients declines in several countries, additional effort must be made to promote education and awareness of health workers about the dangers of reactions and neuritis. There is serious concern that alternatives to prolonged corticosteroid use should be developed. It was also noted that neuropathic pain is not well recognized, with no data on the epidemiology or management of this problem.

Considerations of future research needs regarding T1R and neuritis emphasized that priority should be given to identifying factors that trigger reactions, and that promising areas of investigation might include endocrine influences, the effect of co-infections with other bacteria or parasites, and genetic markers of predisposition to reactions. Speakers noted some promising markers of reaction using PCR primers developed (and patented) in India; preliminary evidence that the plasma level of IPlO might be a useful marker were noted. An overview emphasized that these research needs must be prioritized for those that have the biggest impact, best feasibility, and likelihood of funding.

Pre-Congress Workshop V

"Integration"

Participants

Rosa Castalia F.R. Soares, Brazil; W.S. Bhatki, India; T. Kirubakaran, India; S.A.R. Krishnan, India/Africa; Alexander Thomas, India; Rebecca Thomas, India; Steve Lyons, Geneva; Denis Daumerie, Geneva; Gomes Unarat, Thailand; Kissawat Somwang, Thailand; Joseph Chukwu, Nigeria; Blasdus F. Njako, Tanzania

Introduction

The workgroup met to discuss the following issues:

1. Leprosy situation in the world
2. The concept of integration: are there substantial differences worldwide?
3. Integration of leprosy services in general health services as a strategy to reach elimination
4. Experiences of integration in Africa, India, Americas (Brazil) and Western Pacific
5. Drugs distribution as an essential activity for leprosy integration and sustainability in general health services.

1. Leprosy situation

New case detection was about 250,000 in the year 2006. During the last four years there has been a 20% reduction in new case detection each year. Most of the reduction is attributed to the reduction of new cases in India.

2. Operational definition of integration

There is no universal definition of integration. The general understanding of integration is that the diagnostic and treatment services to leprosy patients are to be provided by the general health services. This should be supported by the referral services, especially or management of POD, and other complications. Provision should be made for physical or social rehabilitation for disabled leprosy affected people, on an integrated basis rather than on a special basis.

3. Quality of services during and after integration

Diagnostic and MDT services through general health services are of acceptable quality. Challenges still remain in areas swch as POD, drug logistics and reporting, particularly when new case detection falls to very low levels.

4. Sustainability of integration

Sustainability remains a matter of great concern, despite the fact that confidence in the general health services remains high. At low levels of endemicity, it is difficult to maintain quality in diagnosis and priority to leprosy activities.

Recommendations

1. Training of GHS staff is a continuous process and there is a need to develop a more standardized curriculum for use at the national level.
2. There is a definite need to design a methodology to validate the epidemiological situation in different areas (e.g. in urban and rural areas).
3. There is a growing need for the redeployment of leprosy vertical staff into other general health services like TB, HIV and community services where appropriate.

4. The availability of MDT at an appropriate level of general health services, to improve patients' access, remains a key element for the effective integration of services.
5. Patients access to MDT needs to be flexible to improve compliance. For example, more than one month's treatment should be offered to patients when requested.
6. Innovative approaches to MDT delivery should be promoted, e.g. postal delivery to individual patients in areas of low endemicity or absence of effective medical services. This method has been used successfully for some drugs in Brazil (HIV & diabetes drugs). This applies also to IEE and the training of general health service staff, using internet based tools (e.g. distance training and medicine).
7. Regular monitoring and periodic evaluation exercises should be carried out using appropriate methodologies, to ensure MDT services are of high quality.
8. Leprosy should be included in the curriculum for Medical, Nursing and Paramedical courses.
9. In view of the fact that leprosy is decreasing in many parts of the world, a core of expertise needs to be maintained at the referral level.
10. Governments, NGOs and communities should work together closely to implement the integration process.

Pre-Congress Workshop VII

"Future Research Needs in Leprosy"

(Chairperson : PSS Rao, Rapporteur : Ruchika Chandra)

About 25 experts participated in this workshop. Four main topics were considered:

Epidemiology & Control, Diagnosis & Classification, Chemotherapy & Chemoprophylaxis, and Prevention of Disability Each of these topics was introduced by a Lead speaker and followed by at least one main discussant before general deliberation by all the participants.

The following research needs have been identified in the four key areas for consideration by stakeholders, research organizations and leprosy institutions as well as by all those concerned/affected by leprosy. There has been no intention to prioritise, but to formulate guidelines of possible research.

A. Epidemiology and control of leprosy

1. *Epidemiology of infection* –This remains a 'Holy Grail' for leprosy epidemiology and control. Right now we lack tools for detailed studies. If the IDEAL consortium comes up with something useful- this would be extremely important.
2. *Role of nasal carriage in transmission* – More work is needed to confirm that the PCR signals really are *M. leprae*, and, if so, to understand the dynamics is carriage persistent, transient, recurrent and does it induce protective immunity.

The implications of how it contributes to transmission and persistence and if it should be a target for control interventions need further study.

3. *Identification of environmental and animal reservoirs of M. leprae* – There is much evidence that armadillos harbour *M. leprae*, but their contribution to infection and disease in humans is still not clear. In addition there are several reports of associations with water, and of *M. leprae* PCR signals in water.
4. *Studies on 'provocation' of leprosy (BCG and HAART)* – There is much evidence that either vaccination (BCG or *Mw*) or HAART can provoke clinical onset of reactions. Understanding the absolute risks and the immunological mechanisms, requires clinico-immuno-epidemiological studies.
5. *What aspect of poverty influences leprosy?* – Many studies have shown that leprosy is associated with poverty, but just what aspect of the poverty complex is responsible for this (hygiene, nutrition, crowding, intercurrent infection etc) remains unclear.
6. *Accurate estimation of relapses and drug resistance* – There is little evidence as yet that relapses or drug resistance are important, but weakened leprosy control programmes will be associated with inadequate treatment, and there is a need to monitor disease recurrences.
7. *Methods to improve Data quality* – All epidemiology and control research is dependent upon good data. There needs to be a concerted effort to insist upon transparency and quality in leprosy data collection at all levels. Interpretation of data should be straightforward and clear. Moreover, data from different regions might have to be interpreted differently.
8. *Methods of strengthening of referral centres* – in areas of diagnosis and advanced treatment.
9. *Identification of the needs of field workers.*

B. Diagnosis and classification

Newer tests that require further research to prove them useful in leprosy:

1. ***Serology*** : Newer antigens that require further research are MMP-II (bacterioferritin)- which is also reactive in PB sera, 35kD protein, other glycolipids like PDIM and GPL and mycolic acids like TMM and TDM. Antigen detection (like Antigen 18) is another new area of research identified instead of antibody detection, as the sensitivity and specificity of serology may be improved.

2. ***Skin test antigens*** **:** New generation of skin test antigens which are more specific than existing ones, such as two new antigen preparations derived from Armadillo -derived *M. leprae* named MLSA-LAM and the second product, *M. leprae* cell wall antigen (MLCWA) need to be looked into.

3. ***Post genomic approach to identify new diagnostic antigens*** **:** After the completion of genome sequencing of *M. leprae* in 2000, genes that are unique to *M. leprae* and have no homologues in *M. tuberculosis* need to be looked into.

4. **PCR and more specifically RT PCR :** For detection on *M. leprae* encoding specific genes or repeat sequences is potentially highly sensitive and specific since it detects *M. leprae* DNA in 95% of multibacillary and 55% of paucibacillary

patients. Other DNA techniques- Transmission by VNTR analysis with the study of more loci, recognized as being variable in leprosy patients. SNPs as diagnostic tools need greater study.

5. ***Other tests*** **:** further research into various chemokines and cytokines for the diagnosis of leprosy and reactions.
6. Further research into non invasive tests such as High resolution sonography, MRI and Nuclear magnetic resonance. They have shown that arterial and venous flow is altered in damaged nerves and in active ENL and are more patient friendly.
7. ***Newer culture methods*** **:** as the older methods of mouse foot pad culture remain time consuming, labour intensive and expensive.
8. Even though most of the above diagnostic tests remain more expensive and out of reach of most people, they should be fme tuned for use in difficult cases.

C. Chemotherapy

1. Further research into newer antimicrobial agents with various degrees of bactericidal activity against *M. leprae* is needed. See table 1.
2. Research into costs and cost- benefit scenarios.
3. Research into further simplification of treatment for better adherence and monitoring. For e.g. the following combination was suggested : RFP 900 mg (or RIP 600 mg) - MXF 400 mg - CLR 1000 mg (or MIN 200 mg), all drugs administered once-monthly under supervision(the dosages are for adults).
4. For the regimen targeting patients with RIF-resistant leprosy-urgent research is needed. One proposed regimen was : an initial 6-month intensive phase followed by an additional 18-month continuation phase:

- ***Intensive phase*** **:** MXF 400 mg - CLO 50 mg - CLR 500 mg - MIN 100 mg, daily for 6 months;
- ***Continuation phase*** **:** MXF 400 mg - CLR 1000 mg - MIN 200 mg, once monthly for an additional 18 months.

5. If preliminary clinical trials demonstrate that the simplified regimen (i.e. the regimen for patients with RIF - susceptible MB leprosy and is administered once monthly for 12 months) is reasonably well-tolerated, and provide early evidence of effectiveness for treating MB leprosy, then the second step of clinical trials i.e. controlled clinical study, should be undertaken.
6. In the controlled clinical study, multiple regimens, including the current MB regimen as positive control should be compared. Each arm of the trial requires at least several hundreds of MB patients, and follow-up of at least 7 years after completion of treatment.
7. Better methodologies are required for accelerate the development of new MDT regimens as the mouse footpad system is technically demanding, time consuming and development of tests for measuring bactericidal activity against *M. leprae* more rapidly and precisely would be helpful.
8. A simple and reliable surrogate marker for measuring the sterilizing activity against *M. leprae*- the most appropriate indicator of the ability to shorten the duration of treatment.

Table 1: Newer drugs displaying bactericidal activity against *M.leprae*

Drug	Class	Bactericidal activity in mice*	Bactericidal activity in human*	Unit cost
Pefloxacin	Fluroquinolone	++	++	Moderate
Ofloxacin		++	++	Moderate
Moxifloxacin		+++	+++	High
Clarithromycin	Macrolide	++	++	Moderate
Minocycline	Tetracycline	++	++	Moderate
Rifapentine	Rifamycin	+++	Not done	High
R207910	Diarylquinoline	+++	Not done	Not commercially available
Linezolid	Oxazolidinone	+	Not done	High

Based on the activity of (+) for dapsone and (+++) for rifampicin.

Chemoprophylaxis: Chemoprophylaxis is feasible only in a strong leprosy control program.

1. Research into more effective regimens is needed for very high risk groups. These groups need to be correctly identified first.
2. Tools to detect sub-clinical leprosy to study tailor-made prophylactic treatment regimens are required.
3. Further operational / health systems research to identify characteristics of the public health system that are critical for a successful implementation of chemoprophylaxis under routine leprosy control program conditions.
4. Regimens of prophylaxis also remains an unexplored area.

D. Prevention of Disability

1. Operational research on making self-care more successful.
2. Research on the role of stigma and self-stigma in de-motivating. people, and conversely on the importance of individual empowerment in giving people a positive motivation, needs to be developed further.
3. Research on the best ways of ensuring adequate access to appropriate footwear, on a country-by-country basis.
4. Reactions and neuritis- Further research into methods of integrating knowledge on reactions and neuritis into the general health services, where the majority of people with leprosy are now treated. Therefore, simplified methods of monitoring, or even self-monitoring by patients themselves, need to be developed and tested, along with straightforward guidelines for referral and management.
5. Neuropathology - there are three major areas for further research- mechanisms of neuropathy in leprosy, diagnosing neuropathy - screening and diagnostic tests and treatment of neuropathy. There is also a need to study early damage in a

research setting, so early diagnosis with more sophisticated, but also more sensitive, tests must also be studied.

6. Further research on optimal dose and duration of steroid treatment. Other immunosuppressant drugs have only been minimally examined so far, need to be studied further.
7. Identification of best practice in the treatment of neuropathic pain in leprosy and the role of nerve decompression surgery.
8. Research into more effective methods of rehabilitation to enable affected persons to be more independent and to increase their social interaction. Stigma reduction- is essential and is an important social concern.
9. Multi centric, multi-disciplinary research on operational issues of "prevention of disability" with comparison between leprosy institutions and the general health systems.

Annexe II: Participants of the Pre Congress Workshop-7

S. No.	Category	Name	Speaker	Area
1	**Convener**	DrPSSS Rao		India
2	**Epidemiology**	Dr Jan Hendrik Richardus	Chief discussant	Netherlands
3		Dr Masanori Kai	Speaker	Japan
4		Dr H Joseph Kawuma	Chief discussant	Africa
5		Dr Paul Fine	Lead speaker	UK
6		Selvasekar Abraham		India
7		Dr Maria Leide de Oliveira		Brazil
8	**Diagnosis and Classification**	Dr Vaneja Shetty	Lead speaker	India
9		Dr Indira Nath	Chief discussant	India
10		Dr Kiran Katoch	Chief discussant	India
11		Dr Murdo MacDonald		Nepal
12	**Chemotherapy**	Dr Baohong Ji	Lead speaker	France
13		Dr Linda Oskam	Chief discussant	Netherlands
14		DrWCS Smith	Chief discussant	UK
15	**Prevention of Disability**	Dr Paul Saunderson	Lead speaker	USA
16		Dr RK Mutatkar	Chief discussant	India
17		Dr Wim Brandsma		Ethiopia
18	**General**	Dr Mohit Mehndiratta		India
19		Dr P Krishnamoorthy		India
20		Dr Ana Claudia		Brazil
21		Dr Jannine Ebenzo		Africa
22		Dr Ruchika Chandna		India
23		DrPKDass		Amsterdam
24		Dr Casabianca		India
25		Dr A Antony Samy		India