

Final

**INFORMAL CONSULTATION ON RIFAMPICIN
RESISTANCE IN LEPROSY**

National JALMA Institute of Leprosy and Other
Mycobacterial Diseases, Agra, India

30th November and 1st December, 2006

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Introduction:

The emergence of drug resistance is a cause for concern and a threat for any infectious disease intervention programme. For leprosy, a chronic disease with social stigma, drug resistance poses a serious impediment at a stage when there is a dramatic decline in prevalence due to intensive and concerted chemotherapy intervention made by the global community. To effectively meet the challenge of containing the disease and sustaining the declining leprosy trend, it is essential to keep a vigil on the drug resistance scenario at many vulnerable settings. This can be done by drug resistance surveillance through an appropriate clinical, field and laboratory support system. The present informal consultation was planned to address these issues.

Objectives:

1. To review the current technology to detect resistance to anti-leprosy drugs.
2. To review recent findings from centres assessing rifampicin resistance.
3. To recommend reliable tools and procedures for surveillance of rifampicin resistance.
4. To consider methods for surveillance of resistance to other anti-leprosy drugs.

Dr. V. M. Katoch outlined the genesis of the meeting as conceived by Dr. V. Pannikar and the importance of this group to address this theme. A multi-centric project underway at the National JALMA Institute for Leprosy & Other Mycobacterial Diseases (NJIL), Agra initiated by Prof. N.K. Ganguly, Director-

General, Indian Council of Medical Research, were outlined. Dr. Katoch also appreciated the commitment of the international community in this process.

Dr. Pannikar welcomed the participants, provided the background and explained WHO's strategy for leprosy control. He felt that continued emphasis of the programme on elimination was resulting in a reduction of interest and funds on the key issues such as, 'Quality care for the patients', 'Capacity building', 'Training' and 'Research'. To meet these challenges, WHO had formulated a new strategy with definite guidelines through the Technical Advisory Group (TAG). He also said that efforts were needed to evolve a treatment policy and seriously consider alternate regimens without rifampicin as and when needed. Individuals and Institutions should continue to concentrate on the research issues pertaining to this aspect.

Prof. W. C. S. Smith, Chairman, TAG, delineated issues on 'maintaining and sustaining leprosy control' since the future of leprosy control could be threatened with the development of rifampicin resistance. Since rifampicin was the core drug in MDT, this was a relevant and important issue. In this context, reviewing current technology for detecting rifampicin resistance would enable programme managers to plan a global surveillance strategy.

In a brief discussion that followed, Dr. Katoch felt that it would be better to discuss the technical and field issues separately. Dr S. T. Cole observed that considering the current developments on the laboratory diagnosis of rifampicin resistance the challenges were mostly logistical than technical. Rifampicin had helped in curing about 15 million patients. Hence, there was every possibility that some patients might have developed resistance to this drug. The two-drug combination of rifampicin-dapsone had been used quite extensively in some countries, for example, in Cuba as early as in 1977 and in Myanmar in the 1980s,

although it was unclear whether the application of the two-drug regimen may have contributed to the emergence of rifampicin-resistant leprosy. Prof. Baohong Ji felt that there were two major components to be considered. One was the laboratory component on rifampicin resistance, which was straightforward and the other was to identify the rifampicin-resistant patients in the field which was often difficult due to several constraints. Prof. M. D. Gupte felt that it was important to understand the mechanism of rifampicin resistance, and the specificity, sensitivity, positive and negative predictive value for the available tools. Dr Vissa D. Varalakshmi mentioned that since the mechanism of rifampicin resistance was known, it was easier to develop an adaptable diagnostic tool.

Prof. Cole¹ made a presentation on the "Molecular basis of rifampicin resistance and methods for detection". He outlined several issues on RNA polymerase, detailing firstly the 3D structure of RNA polymerase consisting of three subunits. He also showed how rifampicin binds to this group and prevents transcription and mutations in the *rpoB* gene thereby leading to rifampicin resistance, specifically by alterations at serine 411, substitution. He further outlined mis-sense mutation seen in *M. leprae* (point mutation in *rpoB* gene). He described in detail the phenotypic methods including mouse footpad method (MFP), BACTEC and molecular methods including PCR-SSCP and DNA sequencing for detecting resistance. He mentioned that Telenti's publication on mutational frequency of rifampicin resistance in *M. tuberculosis* gave valuable information to develop several probes to develop a hybridization assay. This was field-tested by Macdonald in Nepal and confirmed later by DNA sequencing. Further it was validated in Paris, Madagascar and Kathmandu by detection systems using chemiluminescence and calorimetric methods.

Prof. Cole made the following recommendations based on the available evidence:

¹Copies of presentations made during the meeting are attached as Annex-3 to this report.

- Undertake a large-scale prospective field testing study of rifampicin resistance at least at two sites in Asia/ Africa.
- Consider inclusion of detection of DDS and fluoroquinolone resistance which would further enhance preparedness to face rifampicin resistance.
- Use PCR sequencing or its equivalent as this would ensure detection of rifampicin resistance with greater accuracy.

Prof. Smith observed that available evidence indicated that there was a 100% agreement with mouse footpad and molecular methods. Prof. Ji cautioned that only a small number of patients were tested so far and it was safer to say high concordance than full concordance. Prof. Smith opined, considering the cost effectiveness and turn-around time of mouse foot pad, molecular methods would be better considering highly stable genome of *M. leprae*. Dr Gillis endorsed the robustness of molecular tests.

Dr. Varalakshmi presented the practical plans for assessment of drug resistance, clinical response and reactions in leprosy patients in South America. She dealt in detail with the molecular epidemiology, viz. reservoir, patients and environmental factors, and tracking. In terms of drug resistance, she felt including old patients' samples and all new untreated patients or those who were under treatment in leprosarium settings in Colombia would provide adequate material. The magnitude and characterization of leprosy relapses in patients in Brazil including genetic analysis, total number of new and relapsed cases and relapse definition criteria with a clear objective, methodology, sample size based on the level of drug resistance, and parameters that were employed including re-sequencing were some of the issues elaborated by Dr. Varalakshmi.

Molecular methods for detection of drug resistance in leprosy and their need were presented by Dr V. M. Katoch. He outlined the relative merits of each

methodology considering mouse foot pad as a bench mark for comparison. It was followed by some reports on drug resistance in leprosy from India and narration of various available methods. He further explained in detail various available methods like DOT-blot assay starting from PCR SSCP. He also provided detailed information of an ICMR multi-centric study and the findings. Detection of mutations in *rpoB* gene region in *M. tuberculosis* comparing Innolipa and the importance of evaluating the same with in-house assays including the mutation commonly seen in regions other than *rpoB* and low level resistance to rifampicin, mutations seen for other anti-leprosy drugs including quinolones were explained in detail. DNA micro-array assays and limitation of user group employing this methodology in detecting resistance was further explained.

Prof. Smith wanted the group to address the issue of clofazimine resistance considering the emergence of drug resistance to quinolones.

Mr Bishwa Raj Sapkota made a presentation on the development of a novel multiplex PCR method for detecting mutations conferring rifampicin resistance in *M. leprae*. His study was based on the detection of mutation in 81 BP & *rpoB* gene. The description of wild type strains and mutant strains based on three primers that were described by Honore and Cole and evaluation of various sample types including sequencing of some samples, he found that the results obtained using the PCR method was consistent with the MFP and some among them were confirmed by sequencing as well. According to him, these results indicated that this technique can reliably identify rifampicin-resistant strains of *M. leprae* at 531 position. He recommended to extend this study for all rifampicin resistant strains and suggested use of multiplex PCR systems to address the issue of multi-drug resistant (MDR) leprosy.

The necessity to do prospective hybridization on a larger number of samples at least from two sites in Asia and Africa and the need to confirm all results independently by DNA sequencing was emphasized by Prof. Cole. Dr Katoch mentioned that other parameters in regular use at various laboratories should be continued in parallel. Prof Gillis agreed that DNA sequencing should be the standard methodology. Prof Smith described the difference between surveillance and individual patient care and the importance of global surveillance and networking. Dr Paramasivan gave the analogy of the tuberculosis situation and suggested prospective studies on new cases and also including samples from patients with previous treatment history. Since this meeting was about global drug resistance, it was felt that attention should be given to surveillance.

During the discussions, PB smears and high positivity rate with PCR were dealt with by many. Dr Varalakshmi explained their experience with DNA sequencing and limitation observed with PB cases. Inclusion of dapson and fluoroquinolone and the limitation of polymorphism seen with *gyrA* with *M. tb* were described by Dr Katoch. He cautioned that mutation at *gyrA* alone may not cover all quinolone resistance. Prof. Gupte observed that while some aspects were getting clearer, others were not in the general discussion. He questioned the inclusion of quinolones when this drug was not being used for the treatment of leprosy. He felt that by taking the analogy of tuberculosis, there could be limitations such as mismatched data sets and validation of such samples. He further observed that surveillance, which could be part of 'International Health Regulations' under disease surveillance systems, laboratories will be covering most of the issues that were discussed. He emphasized the need to develop disease surveillance and drug resistant surveillance activities in line with these newer developments.

Relapse, re-treatment and drug resistance level and transmission were highlighted by Dr Varalakshmi. Dr .Gillis queried the post-dapson era and primary and secondary drug resistance. Prof. Ji observed that primary dapson resistance started appearing only after 1977. He felt that the magnitude of drug resistance was not clear and felt that well-organized drug resistance surveillance becomes was necessity. At the same, time he cautioned that poor surveillance

was worse than no surveillance. Dr Pannikar wanted a clear understanding on rifampicin resistance to move forward with a definitive global plan especially for the African settings. Prof Cole strongly advised that considering resources, instead of MFP experiment which was far more demanding, it would be advantageous to concentrate on DNA sequencing. He felt specialized sites such as JALMA should be encouraged to continue the MFP studies along with the molecular studies. Prof Ji explained the limitation with the mouse experiment when one was aware of the mutation related to resistance.

Dr Katoch reiterated that to start a surveillance system, routine skin smear and PCR are fine. At the same time, other available parameters should be considered based on their merits along with the mouse foot-pad studies. Dr Katoch explained drug resistance from 1985 onwards at JALMA settings and data were grouped and presented as post-1990 periods. Rifampicin resistance in patients attending OPD of JALMA (1990-2002) was observed in 7 out of 77 patients. He also provided details of a multicentric study on Drug Resistance Survey in leprosy undertaken by an ICMR Task Force wherein 59 biopsies were studied. Screening for drug resistant *M. leprae* using MFP in relapsed MB cases was carried out. Results of 16 biopsies from MFP revealed no resistance. Of the 48 samples in this group none showed mutation in *rpoB*. Two specimens had mutation in fol P1.

Prof. Gillis presented an overview of drug resistance based on screening of patients at Karigiri, South India over the past seven years. He explained the challenges faced on two fronts - operational and technical. The former was important for contacting and managing investigations for patients closer to home and the latter for addressing the question of chemotherapy to reduce drug resistance. During 2000-2006, they identified three patients with drug resistance based on MFP assay and explained its complexity and raised the need for an alternate strategy. He further elaborated on specimen preparation of skin biopsy

material for PCR-DNA sequencing with its sensitivity of 10^3 - 10^4 bacteria and a specificity of 100%. In conclusion, he underlined the importance of establishing standard laboratories and standardizing methodologies to face these challenges.

Dr Masanori Matsuoka presented the prevalence of drug resistance in *M. leprae* and detailed at first the prevalence of drug resistance to rifampicin in Japan in the category of relapse or intractable cases: Total 24 (51%); DDS and RIF: 7; DDS, RIF and FQ 5; DDS alone 8; RIF alone 2 and quinolone alone: 2.

Among the new cases, rifampicin resistance was observed in 4 out of 106 (3.8%), 1 of 15 (6.6%), 0 of 47 (0%) and 0 of 40 (0%) from Indonesia (V. Maluku), Myanmar (Yangon), Philippines (Cebu) and Indonesia (Surabaya) respectively. Among relapse cases, it was 2/9 (22%), 0/36 (0%); 0/15 (0%) and 'not done' at the above mentioned sites. Out of three relapse cases from Nepal, one was rifampicin resistant.

Dr Pannikar explained that before the introduction of standard MDT in Myanmar large numbers of patients were treated with a two-drug combination using dapson and rifampicin. If the patients were dapson-resistant, it amounted to mono-therapy with rifampicin. Dr Gillis felt that the data would be helpful for the selection of surveillance sites. The question of MDT implementation and development of resistance to rifampicin was further discussed at length considering Indonesia was the first country to have received MDT. It also underlined the importance of expanding the studies in these countries at multiple sites. Dr Pannikar emphasized the importance of each of these countries.

Rifampicin resistance in tuberculosis in the community in Andhra Pradesh (4 districts) and Orissa (2 districts) was presented by Dr Aparna (LEPRA, Hyderabad, India). It was similar to the resistance patterns seen in other sites in

India. She also presented details on 160 fine-needle aspirates from lymph nodes and culture results obtained on 50 isolates. Isolates that were resistant to rifampicin were from patients who had previous pulmonary tuberculosis. All these isolates had previous pulmonary tuberculosis. Dr Aparna outlined the number of leprosy cases seen during 2005-06 at Blue Peter's Research Centre. Forty relapse cases were identified. A few case descriptions on clinical and bacteriological responses were presented by her. Dr Aparna thus documented the available capacity and potential at LEPRA, Hyderabad.

Dr C.N. Paramasivan presented in detail the global multi-drug resistance scenario for tuberculosis and gave a progress report on the available drug resistance surveillance data from India in different settings. He narrated the available data on Global Extended Drug Resistance (XDR) TB. He then explained various testing methodologies available for tuberculosis and their merits and also pointed out the training aspects and limitations experienced with regard to human resources. According to him, the lessons learnt from TB could help in planning drug resistance surveillance in leprosy.

Prof Ji presented the "Operational Consideration of Monitoring the Prevalence of rifampicin-resistant leprosy in the population". He narrated the development of resistance in leprosy and explained the reasons for MDT implementation to prevent emergence of rifampicin-resistant mutants. He felt that monitoring rifampicin resistant mutants was imperative since this was the backbone of MDT. To achieve this he underscored the following: augmenting field and laboratory activities; creation of a network; identifying study areas; defining protocols and carrying out surveys. According to him, strong political will, a functional leprosy programme, identification of sufficient number of well-characterized patients, and strong human resources were of paramount importance. He emphasized the importance of quality of skin smears, sites to be chosen for skin smears and good quality of reporting and recording. The importance of quality assurance by

re-analyzing all positive smears and 10% of negative smears was further elaborated. The merits and difficulties involved in mouse footpad technique and PCR-based DNA sequence analysis of *rpoB* Gene as a cost-effective technique were explained. Capacity building of National Reference Laboratories to carry out DNA sequence analysis was also emphasized.

In an extensive discussion on clofazimine resistance it was observed that at present a molecular method to identify clofazimine resistance was not available. Dr Kiran Katoch observed that absence of confirmed clofazimine resistance may perhaps be due to the immuno-modulatory effect of clofazimine and multiple actions of the drug.

Prof M.D. Gupte presented the 'Surveillance of drug resistance: Experiences from other diseases'. He observed that in South India a total of 171,400 individuals were recruited for the multi-arm leprosy vaccine trial during 1990-91 and were followed for about 13 years and the incidence came down from 2.4/1000 to less than 0.6/1000. Only around 100 smear positive incidence cases were detected during this period. He thus emphasized reduced levels of leprosy prevalence and incidence in various field areas and the difficulties in recruiting huge populations in such studies. Prof Gupte defined surveillance as an ongoing and sustainable activity. This can be achieved by having a sentinel population, carefully worked out sample size and appropriate analysis. The process of data collection based on the magnitude of drug resistance, monitoring, capacity building and advocacy could augment this further. Laboratory capacity strengthening and mathematical modelling could predict whether the intense pressure by the quantum of drugs used was responsible for this problem of drug resistance. Networking of laboratories would be the additional key area in surveillance activity which needed to be established.

Prof Smith explained the need for 'reliable tools' based on agreed standard methods, quality, reproducibility and viability. Reliable field procedures to assess various categories of patients based on established definitions were explained further. Eliciting history to identify new cases, sample size, sampling defined area, selection of a control programme, surveillance of trends by planning a prospective annual survey for the next 5-10 years and the importance of concentrating on new cases by including countries in Asia, Africa and America were also explained.

Recommendations:

The participants made the following recommendations:

1. Rifampicin resistance surveillance for leprosy should be established immediately.
2. PCR sequencing for drug resistance studies for rifampicin should be undertaken.
3. Other drugs e.g. dapsone and clofazimine, and other anti-leprosy drugs, not part of the programme (MDT), need to be studied only in specified centres/areas.
4. A surveillance network using different appropriate approaches to detect drug resistance and to assess its trend should be established.
5. The method of choice to carry out PCR sequencing for screening drug resistance should be based by obtaining two separate slit skin smear specimens for each patient (one blade per site); to wash the same blade with 70% ethanol for the isolation of genomic material; to transport material in 1 ml of 70% ethanol; and to preserve all positive and negative slides for quality assurance.

6. The method for isolation of DNA, dehydration was considered to be the most appropriate procedure, either by a freeze-boiling (simple process) or by a physico-chemical method using lysozyme. In fact, any kit-based procedure can be used.
7. For the PCR reaction, it was decided to compare different primer sets at the Institut Pasteur (Dr.S.T Cole) and to choose ideal ones for rpoB, folP1 and gyrA for rifampicin, dapsone and ofloxacin respectively. It was also resolved to use the same primers and master mix (AB1) for PCR and sequencing, as well as a chain termination method for sequencing (AB1); and, finally, for confirmation of mutation by sequencing the second strand.
8. A “Data Bank Sequences” should be created in order to:
 - trace depository for raw data;
 - maintain “Data Bank sequence with patient information”; and
 - create national and international networking.
9. International networking among laboratories needs to be strengthened and support from the Institute Pasteur in facilitating this collaboration is needed following Good Laboratory Practices (GLP).
10. Four protocols addressing the issues of “secondary resistance”; planning both retrospective and prospective studies on “primary resistance”; should be developed and coordination through international networking should be established.
 - As an approach meant for surveillance, the “secondary resistance” studies will be based at referral centres. The study will focus mainly on endemic countries and the results of the investigations will be utilized for patients’ care by employing appropriate feed-back mechanisms. In order to achieve this,

standard clinical information forms will be generated to accompany the samples. Here too, appropriate international networking is planned.

- The “Primary Resistance Retrospective Study” will be designed by identifying prospective centres and inspecting the available materials. Standard clinical information forms to accompany the samples will be generated and appropriate international networking planned.
 - The “Primary Prospective Study” will be carried out within a predefined geographical area where sufficient numbers of new smear-positive cases are available. The importance of this study will depend on the results of detailed clinical history forms that ensure true, new smear-positive status. Sample size calculations and periodic annual surveillance will be planned at these sites.
11. Centres will be identified where previously collected skin smears from leprosy patients are available. Equally sensitive and specific techniques for PCR studies from those smears are available and hence, this available material (previously collected skin smear slide) needs to be used for drug resistance studies.

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JALMA, Agra, India, 30th November to 1st December 2006**

Agenda

Day 1: Thursday, 30th November 2006

- 09:00– 09:30 Welcome address - Dr Vijaykumar Pannikar, Team Leader, Global Leprosy Programme
- Opening remarks - *Chairperson – Professor Cairns Smith*
- Introduction of participants
- 09:30– 10:30 Review of the current technology
- “Molecular basis of rifampicin resistance and methods for detection”. - *Dr S.T. Cole*
 - Discussion
 - “Development and evaluation of reverse-hybridization assays for detection of mutations in the rpoB genes of *M. tuberculosis* and *M. leprae*” - *Dr Ray Cho*
 - Discussion
 - “The mutation detection method based on PCR and hybridization.” - *Dr Masanori Matsuoka*
 - Discussion
- 10:30-11:00 *Coffee break*
- 11:00– 12:30 Review of the current technology (continued)
- “Practical Plans for Assessment of Drug Resistance, Clinical Relapse and Reactions in Leprosy Patients at Locations in South America” - *Dr Varalakshmi / Prof Brennan*
 - Discussion
 - “Molecular methods for detection of drug resistance in leprosy”- *Dr V.M. Katoch*

- Discussion
- “Development of a novel multiplex PCR method for detecting mutations conferring Rifampicin resistance in *M. Leprae*”.- *Mr Bishwa Raj Sapkota / Dr Macdonald*

12:30-13:30 *Lunch break*

13:30–
15:30 Review of the current technology (continued)
- General discussion

15:30-16:00 *Coffee break*

16:00–
17:30 Review of recent findings from centres assessing rifampicin resistance

- Presentation of findings. *Central JALMA Institute for Leprosy and Other Mycobacterial Diseases – Dr Katoch*
- “Overview of drug resistance screening at Karigiri, 1994-2006”
Schieffelin Leprosy Research and Training Centre, Karigiri, India and National Hansen’s Disease Laboratory Research Branch, USA – Dr Thomas Gillis
- Rifampicin resistance in tuberculosis in the community – Andhra Pradesh and Orissa - *Dr S. Aparna, LEPR Blue Peter Research Center, Hyderabad*

Discussion

Day 2: Friday, 1st December 2006

09:00-10:30 Review of recent findings from centres assessing rifampicin resistance
(continued)
Presentation of findings

- Department of Microbiology, Yonsei University College of Medicine, South Korea – *Dr Sang Ray Cho*
- ‘Prevalence of drug resistance in Japan and some Asian countries’,
Leprosy Research Centre, National Institute of Infectious Diseases, Japan – *Dr Masanori Matsuoka*
- Discussion

10:30-11:00 *Coffee break*

- 11:00-12:30 Discussion on appropriate tools and procedures for surveillance of rifampicin resistance
- “The Operational Considerations about Monitoring the Magnitude of Rifampicin-resistant Leprosy in a Population” - *Prof Baohong Ji*
 - “Surveillance of drug resistance: Experiences from other diseases”- *Prof M.D. Gupte*
 - “Reliable tools and procedures for surveillance of rifampicin resistance”, *Prof Smith*
 - ‘Surveillance on rifampicin resistance in tuberculosis and available tools for diagnosis’ - *Dr Paramasivan*
 - Discussion
- 12:30-13:30 *Lunch break*
- 13:30-15:30 Discussion on appropriate tools and procedures for surveillance of rifampicin resistance (continued)
- 15:30-16:00 *Coffee break*
- 16:00-17:30 Recommendation and Conclusion: Next step

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JALMA, Agra, India, 30th November-1st December 2006**

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Presentations made during the

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