

Report of the Workshop on Sentinel Surveillance for Drug Resistance in Leprosy

Hanoi, Viet Nam, 20–22 October 2008



**World Health
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Regional Office for South-East Asia

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Introduction

Professor W.C.S. Smith, Chairman, WHO's Technical Advisory Group on Leprosy Control, welcomed all participants and stressed the importance of this workshop in getting national programmes and reference laboratories to come together to collaborate in setting up a sentinel surveillance system to monitor drug resistance in leprosy. The Vice-Minister of Health, Viet Nam, Dr Nguyen Thi Xuyen, in her opening address welcomed the participants and thanked WHO for the opportunity to host this important workshop in Hanoi. She pointed out that this workshop is an important step towards improving the quality of the leprosy control services and it is very encouraging to see that all partners namely, the national programmes, research institutes and their laboratories and WHO are joining hands to set-up this surveillance system. The WHO Representative to Viet Nam Dr Jean-Marc Olivé addressed the participants and delivered the welcome speech of the Regional Director for the Western Pacific Region.

The participants selected Professor W.C.S. Smith as chairperson, Dr Tran Hau Khang as co-chairperson and Dr Paul Saunderson as rapporteur of the workshop. The agenda and list of participants are provided in Annex 1 and 2 respectively.

1. Setting the stage

1.1 The need to monitor drug resistance

Professor Smith reviewed the history of leprosy chemotherapy and the achievements made during the period of the strategy of Elimination of Leprosy as a Public Health Problem. Looking back at the history of dapsone therapy it was pointed out that as it was used as a monotherapy treatment initially starting with low dosage, secondary dapsone resistance appeared during the mid-1960s and during the 1970s primary dapsone resistance was reported from several field programmes. This led to WHO introducing multidrug therapy (MDT) using three drugs for multibacillary (MB) cases, namely: rifampicin, clofazimine and dapsone. The elimination strategy played an important role in introducing MDT on a wide scale globally, free of cost. It also strengthened integration of leprosy services into the general health care system and improved service coverage in all endemic countries. It introduced simplified diagnosis and classification, increased political commitment and mobilized additional resources for leprosy. In order to maintain the abovementioned achievements the current Global Strategy 2006-2010 has focused its attention towards sustainability and improving the quality of leprosy control services.

It was noted that among the various potential threats that could hinder ongoing efforts to further reduce the burden of disease in endemic countries, the development and transmission of rifampicin-resistant leprosy is potentially a serious threat to the leprosy

control programme. In the past there was a high degree of complacency about drug resistance, mainly because the method available to detect drug resistance, mouse footpad inoculation method, was difficult to perform, complicated, time consuming and expensive. This resulted in a lack of information on drug resistance which, of course, is not evidence of the absence of drug resistance. It was assumed that a combination of three drugs, if taken regularly could prevent the emergence of drug resistance and because reported treatment completion rates were relatively high, it was generally regarded that the self-administered part of the MDT regimen was taken by the patient as prescribed. There is limited information on patient adherence with the unsupervised components of MDT. With the recent development of DNA sequencing methods to detect drug resistance, several reports of rifampicin, dapsone and ofloxacin resistance have been published and this has highlighted the importance of this condition and the need for systematic monitoring.

In addition, although other drugs are available as second-line treatment for drug resistance, their use in the field is perhaps not as simple as MDT and their efficacy and safety needs to be monitored as more patients are put on such treatment. This also highlights the need to develop better alternative regimens. The problem of drug resistance may or may not be acute at present, therefore, it is important that data collection is more systematic and that the trend is monitored carefully so that effective measures to combat this problem can be developed in future.

1.2 Objectives of the workshop:

The objectives of the workshop were to:

- Standardize manuals of procedures for collection, recording, reporting and transporting of samples from each participating centre so as to ensure quality control;
- Standardize methods and procedures for molecular testing of dapsone and rifampicin resistance;
- Standardize procedures for data collection, collation, analysis and reporting of results periodically;
- Facilitate agreement between national programmes, referral institutes and reference laboratories on the procedures for quality control; and
- Strengthen networking and transfer of technology between national programmes and research institutes.

2. Global leprosy situation

Dr Myo Thet Htoon presented the current global leprosy situation, as reported to WHO by 126 countries at the beginning of 2008. He pointed out that globally, new case detection has decreased significantly over the past five years, but in the last two years the

decline has become less steep especially in the South-East Asia Region which accounts for 74% of the global new cases. India detected over 137 000 new cases in 2007 compared to over 139 000 in 2006 which shows a decline of only 1%. Among the top 18 countries (representing 94% of total global new cases) that reported more than 1000 new cases during 2007, 10 countries showed an increase in new case detection compared to 2006. It is noteworthy that though the new case detection is declining globally, the trend at country level especially in the top 18 countries, is not uniform.

Treatment completion rates reported are also high. However, out of 126 countries which submitted leprosy statistics only 16 submitted figures for treatment completion rates, which shows that further efforts are needed to collect this important information. With regard to information on the number of relapse cases, during the last four years approximately 40 countries have been reporting this data with a rather stable total of over 2 400 cases per year. In absolute terms, Brazil, Ethiopia and China reported the highest numbers of relapse cases, but there are questions about the degree of over or under-diagnosis. This is mainly due to the current definition of relapse which is mainly based on clinical signs and the inherent difficulties encountered in the field in differentiating relapse with reactions.

3. Recent reports on drug resistance

Dr M. Matsuoka presented a comprehensive historical overview of drug resistance in leprosy. In 1964, dapson resistance was first confirmed in the mouse-foot-pad (MFP). Clofazimine resistance isolates was reported in three cases since 1982 to 1996, but it has not been reproduced and so can be regarded as negligible. There are no known cases of resistance to minocycline or clarithromycin in *M. leprae*. Resistance of *M. leprae* to dapson, rifampicin and quinolones can be associated to various genetic mutations in the *folp1*, *rpoB* and *gyrA* gene respectively, allowing detection of drug resistant to key components of the multidrug therapy (MDT) by molecular methods with a high degree of accuracy.

Reports of rifampicin, dapson and quinolone resistance have been published by several scientists (Cambau, Cole, Honore, Kai, Lee, Lopez-Roa, Matsuoka, Ozarmagan, Williams and You) in their respective laboratories using molecular biology techniques. Almost all dapson resistant isolates with low degree in MFP test do not reveal mutation in the *folp1* gene but it is of no concern clinically since the mouse dose of 0.0001 gm per 100 gm of diet is far lower than the dose prescribed for a patient. In a recent study carried out among relapse cases by Matsuoka et al, rifampicin resistance was reported from Myanmar (2/24 samples) and Indonesia (2/10 samples). However, none was found in 19 samples collected from Philippines. Dapson resistance was reported in 2/24 samples from Myanmar, 1/10 samples from Indonesia and 5/19 samples from Philippines. Among new or recent cases, rifampicin resistance was reported in 4/121 cases in Indonesia and 1/54 cases in Myanmar. Dapson resistance was reported in 1/121 cases in Indonesia, 4/54 cases in Myanmar, and 2/77 in Philippines.

Amino acid substitutions at the following locations have been observed in the isolates resistant to following anti-leprosy drugs in *M. leprae*.

- Daspone at *folP1*: threonine (AAC) at 53 and proline (CCC) at 55
- Rifampicin at *rpoB*: glycine (CAG) at 407, aspartic acid (GAT) at 410, histidine (CAC) at 420, serine (TCG) at 425 and leucine (CTG) at 427
- Quinolone at *gyrA*: glycine (GGC) at 89, alanine (GCA) at 91, although mutations for serine (TCG) at 92 and aspartic acid (GAC) at 95 have not been detected, these mutations probably confer quinolone resistance according to the findings in *Mycobacterium tuberculosis*

4. Recent advances in DNA sequencing: molecular methods for detection of drug resistance

Professor Emmanuelle Cambau presented further information about molecular methods. The basic concept is that the genotype (mapped by molecular methods) predicts the phenotype, which is measured by the mouse-foot-pad method. Various studies have shown the high concordance between the MFP results and molecular methods, the main exception relates to low-level resistance to dapson, not detectable by molecular methods, which is thought to be clinically insignificant. One study showed 97% concordance for rifampicin resistance with MFP method. A major disadvantage with the MFP method is the lack of growth of the bacilli in a significant proportion of cases, not to mention the practical difficulties of the technique.

Resistance to all current anti-leprosy drugs (except clofazimine) can be linked to specific gene mutations. The molecular methodology involves amplification of the DNA from the specimen by PCR, followed by DNA sequencing and checking for mutations against a known database. Although DNA sequencing is the standard method, if available, various simpler methods are being developed. Professor Cambau is developing a DNA strip method that might be used in the future instead of DNA sequencing. Professor Cambau suggested that the numbering system for gene sequencing needs to be agreed upon (using either the *M. leprae* or *E. coli* numbering systems) as well as a common database of relevant mutations.

Discussion centred on various practical matters, including the type of specimen which should be used (biopsy or skin smear). Further discussion favoured the less invasive procedure of skin smear as the norm; although a biopsy could be done if possible in addition to skin smear, should this be acceptable to the patient. It was suggested that the bacteriological index (BI) needed to guarantee a definite result was a BI of 3+ or more. However, it was suggested that any relapse should be tested, even if the BI is below 3+, as a valid reading may still be possible. For the purpose of starting a sentinel surveillance network for drug resistance which will be initially looking at MB relapse cases as a potential risk group, the experts have suggested including MB relapse cases with a BI of at least +2. This would give a high probability of successfully extracting DNA from skin

smear samples and completing a successful DNA sequencing result. The possibility of mixed populations of bacilli was mentioned, with the suggestion that the MFP method may cope better with this problem than the molecular methods, but this is not known for certain.

As the technology for extracting DNA from skin smear samples improves, a review will be made regarding additional patient inclusion criteria for drug resistance surveillance, for example other risk groups such as defaulters and new multibacillary cases.

5. Country presentations: current practices for diagnosis, referral and management of relapses

5.1 Brazil

Dr Samira Bühler gave a presentation on current practices regarding diagnosis, referral and management of relapses in Brazil. Guidelines on the diagnosis and management of relapse have been available since 1998 and regular meetings are held to keep staff aware about relapses. The criteria for MB relapse are based on appearance of new lesions or exacerbation of old lesions along with newly affected nerves supported by a positive BI and active MB pattern histopathological report. All reported relapses are supposed to be checked at the state level, but this may not always be applied in the field. In a recent study of 142 suspect cases of relapse, only 104 cases were confirmed which included cases treated with dapsone monotherapy also. The proportion of all cases that are designated as relapses rose from 2.5% in 2001 to 3.6% in 2007, but the validity of these figures is questionable.

Since 2006, a case-control study of relapse is being conducted in five States involving seven centres. The study applies clinical, histopathology, molecular methods, MFP studies and serological test (PGL-1) to confirm relapse and identify drug resistance.

5.2 Ethiopia

Dr Elizabeth Kassa presented the situation in Ethiopia. A stable number of 4000 to 5000 new leprosy cases are being detected each year and approximately 7% are children, 12% have grade 2 disabilities and 80-90% are classified as MB. There is only one specialized hospital for leprosy in the country, namely, ALERT, founded in 1965, which currently diagnoses about 400 new cases per year. In addition, 1200 leprosy cases with complications are seen per year and about 500 of them are cases referred from the regions for management of complications.

The Armauer Hansen Research Institute (AHRI) was established in the same compound in 1966 for research in leprosy. It has contributed a lot for expansion of knowledge in leprosy.

Countrywide, around 200 to 300 MB relapses and 4 to 26 PB relapses are identified each year. In Ethiopia, PB cases that develop MB leprosy after completing PB-MDT are not classified as a relapse case but categorized as a misclassified case.

There was discussion about referring to relapse cases in relation to (or even as a proportion of) new cases detected in any particular year. Clearly there is no direct relationship between relapse cases and current new cases, but it may be helpful to indicate the breakdown (i.e. new case, relapse, return from default, etc.) of all cases starting treatment each year, to show drug requirements and as a general indication of the situation.

5.3 India

Dr P. L. Joshi shared the current situation in India regarding relapses. The national guideline has instructed that the suspected relapse cases in the peripheral clinics should be referred to secondary and tertiary levels for confirmation. Once confirmed, relapse cases are to be put on MDT as per WHO operational guidelines. As of August 2008, 277 cases were suspected to be a case of relapse at the PHC level, out of which 182 cases were confirmed at the district hospitals as a relapse. Dr Joshi stated that laboratory services are being utilized at secondary and tertiary level institutions for confirmation of relapses. A reporting system has been developed in the country for monthly reporting of suspected and confirmed relapse cases routinely. On the issue of priorities, Dr Joshi stated that surveillance of drug resistance and establishing the need for effective and safe new drug regimens is the felt need of today.

The experience of the 18 Leprosy Mission Hospitals in India, with a total of 1089 beds available for providing care to persons affected by leprosy was presented by Dr Rajan Babu. The hospitals are detecting around 5 000 new cases a year and admit around 10 000 patients for treatment of complications and for reconstructive surgery. The Stanley Browne Laboratory at New Delhi is the main laboratory supporting these hospitals in providing facilities for various histopathological and immunological tests. The criteria used for diagnosing a case of relapse are based on WHO Operational Guidelines. In 2007, three MB relapses after treatment were diagnosed in the above-mentioned centres. During January to June 2008, three cases were diagnosed with relapse.

Dr Mannam Ebenezer shared experiences from the Scheffelin Institute of Health Research and Leprosy Centre in Karigiri, Tamil Nadu. The institute detects around 250 new cases each year with 80% of them MB cases. From 2004 to 2007, drug resistance studies for dapsone and rifampicin were carried out using MFP and molecular studies. Out of 107 untreated new MB patients with a BI of more than +2 none showed resistance to either dapsone or rifampicin using molecular methods. However, five showed dapsone resistance at high concentrations by MFP methods. Among the group of 22 new cases (that were never previously treated with MDT, then put on MDT at the start of treatment but later did not show one log decline in BI after 12 months of MDT) no drug resistance was found either with MFP or molecular methods. However, among seven cases of suspected MB relapse one patient showed dapsone resistance by both

molecular methods and MFP (at high concentration). There was some loss of concordance between the MFP (which also showed dapsone resistance in five of the new cases – primary resistance) and molecular methods, but there may have been weaknesses in the protocols for administering dapsone to the mice.

5.4 Myanmar

Dr Kyaw Kyaw presented the situation in Myanmar. It was pointed out that Myanmar had a very high number of cases and the cumulative number of patients that were treated with MDT was about 270 000 cases. This meant that the potential for detecting relapse is very high and in addition, around 1000 new cases were treated with a combination therapy of rifampicin, ofloxacin and minocycline (ROM) as part of a WHO clinical trial during the mid-1990s. There are two referral hospitals for leprosy, one near Mandalay and one in Mawlamyaing, and two special skin clinics which are part of the tertiary care hospitals in Yangon and Mandalay. The above-mentioned four centres are regarded as referral centres supporting the integrated leprosy control services operating in each township.

In 2007, a total of 22 relapse cases were reported. At the Central Special Skin Clinic in Yangon General Hospital, 106 relapse cases have been diagnosed during the period of 1990 and 2007, including one multi-drug resistant case. Two early relapses (after 1 and 8 years, respectively) have been noted in a cohort of 200 MB cases treated with 1-year MB-MDT, but no drug resistance mutation was identified in the PCR study. Suspected relapse cases are identified in the periphery, reviewed and confirmed at regional level and in some cases where the diagnosis of relapse is still uncertain cases are referred to the referral centres in Yangon and Mandalay for confirmation. Criteria for relapse are based on finding new skin lesion and new nerve involvement and/or extension of previous lesion with signs of activity. An increase in BI is regarded as the key indication of the multiplication of *M. leprae*, and the Morphological Index (MI) is also considered a useful additional tool in the diagnosis of relapse. An important issue generally faced in the programme is the lack of clinical experience among clinicians as well as specialized leprosy workers in the peripheral units, so that reaction cases may be misdiagnosed as relapse and treated with MDT.

5.5 Viet Nam

The leprosy situation in Viet Nam was presented by Dr Tran Hau Khang. It was highlighted that the new case detection in has declined quite steeply since 1997 from 3.65 to 0.66 per 100 000 in 2007. During 2007, 552 new cases were detected with a MB proportion of 68% and a children's proportion of 4.5%. The MB proportion has increased to between 60% and 70% in recent years. The grade 2 disabilities proportion remains high at 16% to 18%. Interestingly, the actual number of cases with grade 2 disabilities was constant from 1983 to 1998 at around 600 per year, but it has decreased since then and has halved in the last five years, from over 200 in 2002 to 102 in 2007, although the proportion has remained the same because the number of new cases is also declining.

Relapses range from 2 to 27 cases per year over the last nine years. During 2007, eight relapse cases were reported; all of them were MB cases. As of end of June 2008, six MB relapse cases have been reported. In addition, there have been 13 relapses following chemotherapy trials on various regimens of ofloxacin.

Currently, relapse cases are being confirmed at the regional dermatological hospitals and by the National Institute of Dermatology and Venereology (NIDV) at Hanoi.

6. Laboratory aspects on surveillance for drug resistance

6.1 Ethiopia

Dr Demissew Beyene presented functions and activities of the Armauer Hansen Research Institute (AHRI) in Addis Ababa, Ethiopia. AHRI is a well-established research centre performing research mainly on mycobacterial diseases and currently it is administratively linked with the ALERT hospital and it has its own Scientific Advisory Board (SAB). AHRI has a functional network within ALERT campus and with different universities in Ethiopia, the National Tuberculosis and Leprosy Team (NLT), nongovernmental organizations (NGOs) and regional health activities. It has consortium, collaborative and student projects. These projects involve different study sites throughout the country studying TB, leprosy, leishmaniasis, malaria and meningitis, and make a significant contribution to training at various levels, including PhD candidates. There is no current study of drug resistance in leprosy, but the capacity (both in terms of human resources and physical infrastructure) to be involved in the proposed surveillance project is present. Specifically, AHRI scientists have plenty of experience with PCR and equipment is available. AHRI has the experience of receiving samples as to the Standard Operation Procedure (SOP) from different study sites and also sending samples overseas for quality control purpose as well as when there is a gap in technology. Availability of data management unit for data entry, data cleaning and data analysis is an additional advantage. Therefore, the experience and capacity of AHRI justifies its potential to be a partner for the global sentinel surveillance of drug resistance in leprosy being a referral laboratory within Ethiopia.

The possibility of training a scientist in Dr Matsuoka's laboratory was discussed and it was agreed that this could be done as long as AHRI can find funds for this scientist's travel and stay in Tokyo. However, for this current sentinel surveillance to start moving forward in Ethiopia it is important that samples be sent to Professor Emmanuelle Cambau's laboratory in Paris for DNA sequencing while the laboratory in AHRI gains more experience in the technique. The representative from the national programme was unable to attend this meeting, therefore, WHO will approach the national authorities for their willingness to participate in the surveillance network. In the latter the interim arrangements made to get skin smear samples tested in Professor Emmanuelle Cambau's laboratory will be explained. This can continue till AHRI can perform the tests in Addis Ababa.

AHRI will also help in linking up with other referral hospitals in Ethiopia that can be designated as additional national sentinel sites in the future. At present ALERT will be the proposed sentinel site where relapse cases will be diagnosed and managed along with systematic collection of skin smear samples for molecular testing.

6.2 India

Dr Rupendra Jadhav explained about the set-up of the Stanley Browne Laboratory (SBL) which is based at the TLM Community Hospital in Shahdara, Delhi. The laboratory supports a large network of hospitals in endemic areas with PCR capabilities and excellent collaborative links within India and abroad. SBL has also been involved in different research projects where protocols for clinical sample collection from field areas, storage and transport were developed and executed. SBL will be coordinating sample collection, process samples for DNA extraction and carry out PCR amplification. For the DNA sequencing part of the process, it will be sub-contracting this work either to a national facility in New Delhi (at a reasonable cost with a turnaround time of about four days) or it will link up with Central JALMA Institute for Leprosy and Other Mycobacterial Diseases in Agra, India.

DNA sequencing for other research purposes has been out-sourced to private laboratories in the developed countries routinely as it has been found to be cost-effective. Similar innovative approaches could be tried out under the current surveillance system in India as the technology for DNA sequencing is readily available in many government institutes and private laboratories. It was noted that quality control could also be easily built into the project design.

The Central JALMA Institute for Leprosy and Other Mycobacterial Diseases is also another reference laboratory which has agreed in principle to participate in the surveillance system. Studies on drug resistance are currently being carried out at this institute using DNA sequencing techniques. Along with the laboratory at the Schieffelin Institute of Health Research and Leprosy Centre in Karigiri, Tamil Nadu, the laboratories will be coordinating the testing of samples for drug resistance. The laboratory at Schieffelin Institute of Health Research and Leprosy Centre will also be out-sourcing DNA sequencing tests.

6.3 Japan

Dr Matsuoka described the procedures used in his laboratory in Tokyo for DNA sequencing based on samples collected by standard slit skin smears as outlined in the surveillance guidelines. He highlighted the importance of using a stainless steel blade in taking slit skin smears to prevent rust and preserving the samples in 1 ml of 70% ethanol. There is no need to keep samples in a refrigerator and it is regarded as non-infectious for shipping purposes as it is preserved in 70% ethanol solution. A possible alternative is the use of FTA card (similar to filter paper) which has been known to preserve DNA very well. The usefulness of FTA card for this surveillance will be tested in field settings in a few endemic countries.

Steps in the protocol for extracting DNA were presented. This is based on the agreed protocols outlined in the research projects carried out under other research initiatives. Procedures for direct PCR sequencing using the Big Dye 1.1 Terminator Ready Reaction Mix were outlined. Sequencing results were shown and a case of silent mutation was illustrated.

6.4 Brazil

Dr Philip Suffys presented the work done at the Oswaldo Cruz Foundation's Laboratory of Molecular Biology Applied to Mycobacteria in Fiocruz, Rio de Janeiro, Brazil. Recent work on strain typing has been carried out at Fiocruz based on three basic methodologies. There are phylogenetic markers indicated by a number of single nucleotide polymorphisms (SNPs). Strain typing by variable number of tandem repeats (VNTR) has been studied in various centres and has performed well in studies in Brazil. It was noted that it is important that all groups use the same reagents, which vary greatly in cost, to get reliable results. The third method of distinguishing strains of *M. leprae* is through the study of drug resistance.

Currently, work is being carried out on a series of 196 samples from a set of relapse cases and so far two mutations have been found, neither of which was associated with resistance. Some paired samples (initial infection and relapse) have indicated the likelihood of re-infection in several cases, indicated by mutations in the *gyr-A* gene.

Experts at the meeting in Agra, India in November 2006 agreed that the use of DNA sequencing technology and identifying mutations at specific locations will be the method of choice for predicting drug resistance. Based on this recommendation the participants agreed that for the surveillance of drug resistance, DNA sequencing will be the only test used. However, individual participating reference laboratories may carry out MFP studies in addition to DNA sequencing.

7. Discussions on the guidelines for global surveillance of drug resistance in leprosy¹

7.1 Introduction to the objectives and outline of sentinel surveillance

Professor Smith initiated discussion on the Guidelines, currently in draft form. The main components of the surveillance system were explained. The overall aim is to establish a network (based on the participants of this workshop) and monitor trends in secondary drug resistance (rifampicin, dapsone and ofloxacin).

Issues relating to improved reporting of relapse cases at the national level, selection of sentinel sites, need to standardize case ascertainment and definitions, operational

¹ "Guidelines for Global Surveillance of Drug Resistance in Leprosy: Available as a separate WHO document.

issues (patient consent, sample collection, storage and transport) and establishment of a global network focusing especially on the linkages between the referral centres and the respective reference laboratories were presented.

The sentinel sites should be in the key leprosy endemic countries and should have clearly defined catchment areas that were representative of the country. The areas need to have treated a reasonably large number of cases in the previous decade to ensure a minimum number of relapse cases for surveillance. In addition, a referral centre capable of good quality clinical standards and skin smears, and the ability to follow-up patients will be necessary.

The target group as a start will be MB relapse cases as at present it is only secondary drug resistance that the surveillance system will be looking at. Later, as more information on secondary resistance is obtained other risk groups such as defaulters and new cases (for primary resistance) could be considered for inclusion into the surveillance system.

7.2 Definitions and procedures

Dr P. Saunderson explained the various categories of relapse, related to the time elapsing since completion of MDT. After discussion the following groups were agreed:

- PB case – relapsing as PB – this group, while common, is not part of the current study
- PB case – relapsing as MB at any time:
 - New skin lesions (more than five lesions in total) and/or a positive BI
- MB case – relapsing as MB at any time:
 - New skin lesions, and/or an increase in BI of 2 or more units at any single site
 - Exclude Type 1 reaction, especially if within five years of completion of treatment.

A relapse is defined as the re-occurrence of the disease at any time after the completion of a full course of treatment with WHO recommended MDT. Relapse is diagnosed by the appearance of definite new skin lesions and/or an increase in the bacillary index (BI) of two or more units at any single site compared to the BI taken at a same site at a previous examination. Care should be taken to exclude patients suffering from leprosy reactions.

The criteria for inclusion of MB relapse cases in the sentinel surveillance was defined as a person who was initially classified as an MB case and has taken at least 12 monthly doses of MB MDT as recommended by WHO and who is now showing signs and symptoms of relapse and has a BI of +2 and above without any evidence of lepra-reaction. A BI of +2 was suggested, taking into consideration the present limitations in extracting DNA from tissue specimens with low bacterial load.

7.3 Protocol for collection and transporting of samples

The routine procedures practiced in Myanmar in collecting samples and transporting them were presented by Dr Kyaw Kyaw. At the time of diagnosing a case of relapse at the referral centre a verbal consent was taken from the patient to carry out a slit skin smear as part of the routine management procedure of a case. It was a practice to take slit skin smear samples from four sites where the highest BI was found in the previous examination. There was agreement that the number of sites from which skin smears are to be collected for extracting DNA could be reduced to two sites only. The blade was then placed in the micro-centrifuge tube (2ml O-ring tube) containing 1ml of 70% ethanol, which was labelled and stored.

The group agreed that the code numbers for samples from the various participating referral centres should start with the country code used in the telephone directory. It was also suggested that the case report forms be typed for easy reading. The delay in sending specimens to the reference laboratories is not important technically, but should be minimized for the credibility of the programme.

The specimens are not regarded as infectious and as a result shipment of samples can be done using international courier services. National programmes will be using the courier service available for shipment of samples to the reference laboratories.

7.4 Laboratory procedures

The following are the main outcomes of the group discussion:

- The experts agreed that the number of sites from which skin smears are to be collected for extracting DNA could be reduced to two sites only.
- It was agreed that the stainless steel blade used in taking the skin smear should not be left in the ethanol tube. This is to prevent the blade from getting rusty especially when samples are stored for a long period as it could interfere with the DNA extraction process later. The skin smear scrapings attached to the blade are to be washed off using the 70% ethanol solution contained in the tube.
- The group also agreed to use the same PCR procedure and the PCR primers designed by Dr Matsuoka. It was suggested that three genes *folP1*, *rpoB* and *gyrA* will be studied, for dapsone, rifampicin and quinolone resistance.
- Experts representing various reference laboratories agreed to provide DNA sequencing results in two separate reports. One report will be provided by the laboratories to the referral centre where the relapse patient is located and where the patient's basic results of the test will be provided. The report will state giving the basic results as:

- (a) mutations for resistance to either rifampicin, dapsone or ofloxacin present,
 - (b) no mutations for drug resistance present, and
 - (c) no positive PCR products from sample.
- The second report will be more detailed, to be sent to the surveillance network, giving the whole sequence. This would help to build up a database on DNA sequencing which would allow monitoring of new mutations.
 - Quality control of the participating reference laboratories will be arranged with known samples provided by Dr Matsuoka and Dr Stewart Cole from the Global Health Institute, EPFL Department of Immunology, Lausanne, Switzerland. Checking of samples from field laboratories will be done by Dr Stewart Cole.
 - Good liaison between sentinel sites and the laboratory is needed. In the case of DNA negative samples, specimens may need to be sent again. Discussion about sending additional specimens should be agreed upon on a case-by-case basis.

7.5 Management of relapses with rifampicin resistance

Dr P. Saunderson introduced the topic on management of relapses. Treatment of relapse cases without proven rifampicin resistance should be treated with standard MDT, whether or not dapsone resistance is present. It was agreed to standardize treatment for cases diagnosed as rifampicin resistant according to the Seventh WHO Expert Committee Report recommendations, using clofazimine, ofloxacin and minocycline. However, minocycline is contraindicated in children less than 12 years, while ofloxacin is also contraindicated in children and adolescents; both are contraindicated in pregnant women. Though the occurrence of drug resistant leprosy is regarded as a rare event in children under 10 years, as newer drugs for second-line treatment become available, appropriate and safe treatment regimens for children and pregnant women must be developed as a priority research area.

Relapse cases provided with second-line treatment for drug resistance are to be closely supervised and monitored. The exact mechanism is to be decided by the clinician in charge of treating the case at the referral centre. Frequent contact with the clinician in charge will play a crucial part in ensuring regularity of treatment. However, it was noted that close supervision will depend very much on the local situation including the patient's ability to travel regularly to the referral centre. If needed, hospitalization and/or frequent home visits by the health supervisors should be considered. Referral centres are to be provided with funds to cover patient costs, drugs for second-line treatment and supervision purposes.

7.6 Case reporting forms

Dr Myo Thet Htoon introduced the draft Case Report Forms. This form does not include the patient's name for reasons of privacy. Various details were discussed to simplify the forms further. Based on the recommendations from experts regarding obtaining sufficient sample for DNA sequencing from each relapse case it was agreed that skin smear samples are to be collected from only two sites with the highest possibility of providing high BI. It was agreed that the forms should be tried out and reviewed at the next meeting based on the experience gained in the field.

7.7 Sentinel sites currently participating in the global drug resistance surveillance

Code*	Country	Sentinel sites	Reference Laboratory**
55	Brazil	<ol style="list-style-type: none"> 1. Laboratório de Hanseníase – FIOCRUZ , Rio de Janeiro/RJ. 2. Centro de Referência em Dermatologia Sanitária Dona Libânia, Fortaleza – CE. 3. Fundação Alfredo da Matta, Manaus – AM 4. Instituto Lauro de Souza Lima, Bauru/SP. 5. Centro de Referência Estadual em Dermatologia Sanitária em Hanseníase 	<ol style="list-style-type: none"> 1. Laboratório de Hanseníase, Instituto Oswaldo Cruz (IOC), FIOCRUZ, Rio de Janeiro 2. Instituto Lauro de Souza Lima, Bauru 3. Centro de Referência Estadual em Dermatologia Sanitária em Hanseníase, Uberlândia
251	Ethiopia	<ol style="list-style-type: none"> 1. Dermatology Department, ALERT Hospital, Addis Ababa. 2. Armauer Hansen Research Institute (AHRI) Addis Ababa. 	National Reference Centre on Mycobacteria, Faculte de Medicine Pitie-Salpetriere, Paris, France
91	India	<ol style="list-style-type: none"> 1. TLM Community Hospital, Shahdara, New Delhi. 2. JALMA, Agra 3. Hospital of Schieffelin Institute of Health Research and Leprosy Centre, Karigiri. 	<ol style="list-style-type: none"> 1. Stanley Browne Laboratory, New Delhi. 2. JALMA, Agra 3. Laboratory of Schieffelin Institute of Health Research and Leprosy Centre, Karigiri.
223	Mali	Centre for Vaccine Development-Mali (CVD-MALI), Ministry of Health, CNAM-ex-Institut Marchoux, Bamako.	National Reference Centre on Mycobacteria, Faculte de Medicine Pitie-Salpetriere, Paris, France

Code*	Country	Sentinel sites	Reference Laboratory**
95	Myanmar	1. Central Special Skin Clinic, Yangon General Hospital 2. Special Skin Clinic, Mandalay General Hospital Mandalay	National Institute for Infectious Diseases, Leprosy Research Centre, Tokyo, Japan
84	Viet Nam	National Institute of Dermatology and Venerology, Hanoi	1. Department of Microbiology, Yonsei University College of Medicine, Seoul, South Korea 2. National Institute for Infectious Diseases, Leprosy Research Centre, Tokyo, Japan
01	To be identified	To be identified	National Hansen's Disease Programs Laboratory Research Branch, Baton Rouge, USA.

* Given according to international telephone code for country

** Dr Stewart Cole from the Global Health Institute, Ecole Polytechnique Federal de Lausanne, Department of Immunology, Lausanne, Switzerland, has kindly agreed to assist with quality control issues.

As the surveillance expands new sentinel sites as well as new reference laboratories are to be added to ensure geographic representation and to increase sample size. The participating reference laboratories agree in principle to test samples from any new sentinel site free of cost. To ensure quality of the test results it was recommended that in large countries several centres of excellence that have experience in carrying out DNA sequencing studies be selected.

8. Conclusions and recommendations

The following were the conclusions and recommendations emanating from the workshop:

- (1) The revised guidelines for Surveillance of Drug Resistance in Leprosy were approved for implementation. Based on further advances in research, revisions to the guidelines are to be made in consultation with all partners and experts.
- (2) The workshop recommended that the programme of surveillance be started as soon as the agreements from the respective national authorities are obtained. The Global Leprosy Programme will collect case reports forms from the participating sentinel sites on a six-monthly basis. These will be collated and published in the WHO's Weekly Epidemiological Record.
- (3) Additional sentinel sites are to be included in the surveillance system in order to achieve larger sample sizes and better geographic representation. Similarly, additional reference laboratories are also to be included to improve coverage of the surveillance system.

- (4) The workshop recommended that a meeting be held annually to review progress and to update recent advances in DNA sequencing technology among all the partners. It was tentatively agreed that the next meeting will be held on 26-27 October 2009 at a venue to be decided by the Global Leprosy Programme.

Annex 1

Agenda

Monday, 20th October 2008

- 09.00-09.30 hours
- Welcome by Chairperson
 - Opening address by the Vice Minister of Health, Viet Nam (*Dr Nguyen Thi Xuyen*)
 - Message from WR Viet Nam (*Dr Jean-Marc Olivé*)
 - Selection of co-chairperson and rapporteur (*Dr Myo Thet Htoon*)
 - Introduction of participants by (*Dr Myo Thet Htoon*)
- 10:00-10:30 hours
- Why we need to monitor drug resistance? (*Prof. W.C.S. Smith*)
- *Discussion*
- 10:30–11:00 hours
- Global leprosy situation (*Dr Myo Thet Htoon*)
- *Discussion*
- 11:00–11:30 hours
- Summary of recent reports on drug resistance (*Dr Masanori Matsuoka*)
- *Discussion*
- 11:30–12:00 hours
- Recent advances in DNA sequencing for the detection of drug resistance (*Prof. Emmanuelle Cambau*)
- *Discussion*
- 12:00–12:30 hours
- Country presentations: Current practices for diagnosis, referral and management of relapses** (20 minutes per country)
- Viet Nam (*Dr Tran Hau Khang*)
 - Brazil (*Dr Samira Buhner*)
 - Ethiopia (*Dr Elizabeth Dizaneh Kassa*)
 - India (*Dr P.L. Joshi / Dr Rajan Babu and Dr Mannam Ebenezer*)
 - Myanmar (*Dr Kyaw Kyaw*)
- 14:00 –16:00 hours
- Current practices for diagnosis, referral and management of relapses (continued)
- 16:30-17:30 hours
- Current practices for diagnosis, referral and management of relapses (continued)

Tuesday, 21st October 2008

Laboratory aspects: current practices in receiving, processing, testing and reporting on specimen received from the field

09:00-09:30 hours Ethiopia: (*Dr Demissew Beyene*)

09:30-10:00 hours India: (*Dr Rupendra Jadhav*)

10:30-11:00 hours Japan: (*Dr Masanori Matsuoka*)

11:00-12:30 hours Brazil: (*Dr Philip Suffys*)

Discussion on Guidelines

14:00-14:30 hours Introduction to the objectives and broad outline for Sentinel Surveillance for Rifampicin and Dapsone resistance (*Prof. W.C.S. Smith*)

➤ *Discussion*

14:30-15:30 hours Definition and procedures (*Dr P. Saunderson*)

➤ *Discussion*

15:30-16:00 hours Protocol for collection and transporting of samples (*Dr Kyaw Kyaw*)

➤ *Discussion*

16:30-17:30 hours

Group discussions

Group 1. Programme aspects

Management of relapses with rifampicin and/or dapsone resistance (*Dr P. Saunderson*)

Case reporting forms and procedures for data collection, collation, analysis and reporting of results periodically (*Dr Myo Thet Htoon*)

➤ *Discussion*

Group 2. Laboratory aspects

DNA sequencing protocol (*Dr Masanori Matsuoka and Prof. Emmanuelle Cambau*)

Wednesday, 22nd October 2008

Discussion on Guidelines (continued)

- | | |
|-------------------|--|
| 09:00-09:30 hours | Report of the group work
➤ <i>Discussion</i> |
| 09:30-10:00 hours | General discussion on future expansion of the sentinel surveillance to other sites |
| 10:30-11:30 hours | Drafting of conclusion and recommendations |
| 11:30-12:30 hours | Finalizing conclusions and recommendations |
| 14:00-14.45hours | Closing of the Workshop |

Annex 2

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The WHO strategy for reducing the leprosy burden in endemic countries based on timely detection of new cases and their treatment with effective chemotherapy in the form of multidrug therapy (MDT) has been very successful. However, recent evidence on the emergence of *Mycobacterium leprae* strain resistant to the most important component of the standard MDT, i.e. rifampicin, has been a cause for great concern among experts and programme managers. The situation, if left unchecked, is likely to lead to a significant setback in the efforts at controlling the disease in the coming years. The report summarizes outcomes of the Workshop on Sentinel Surveillance for Drug Resistance in Leprosy at Hanoi, Viet Nam on 20- 22 October 2008.



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