1. INTRODUCTION

The fifth meeting of the WHO Technical Advisory Group on Elimination of Leprosy (TAG) was held in Yangon, Myanmar, immediately after the third meeting of the Global Alliance for welcomed participants. He thanked the Government of the Union of Myanmar and the Ministry of Health for hosting these meetings. Dr Daumerie praised the commitment and determination of Myanmar's national programme in overcoming many challenges to reach the elimination goal.

Dr Marijke Becx-Bleumink, Chair of TAG, added her appreciation to the Government of the Union of Myanmar. Introducing participants, Dr Becx-Bleumink welcomed Professor Paul Fine[1] as a new TAG member and Professor Stewart Cole as an invited expert for this meeting. TAG members were requested to take into consideration the reports and recommendations of three important meetings related to leprosy that had taken place during 2002: the ILA Forum on Leprosy, in Paris, France, the International Leprosy Congress, in Bahia, Brazil and the TDR Scientific Working Group, at WHO headquarters, in Geneva. The agenda for the meeting was approved.

2. REPORTS ON THIRD AND FOURTH TAG MEETINGS

During 2002, two TAG meetings had been held. The third meeting was held at Brasília, Brazil, in January 2002. During this meeting many important recommendations were made, including one for a simplified integrated surveillance system, the use of Accompanied MDT to increase cure rates, approval to undertake research to study the efficacy of a Uniform MDT regimen for all types of leprosy and, the need to focus on detection trends in the future.

The fourth TAG meeting, held at WHO headquarters, Geneva, in June 2002, mainly reviewed the protocol for the Uniform-MDT (U–MDT) research study and agreed on the timetable for its implementation. Reports of both these meetings were approved by members.

3. GLOBAL SITUATION AND REMAINING CHALLENGES

Among the 122 countries where the disease was considered endemic in 1985, 110 have now reached the elimination goal at national level.[2] At the beginning of 2003, 12 countries have yet to reach the elimination target. These are: Angola, Brazil, Central African Republic, Congo, Côte d'Ivoire, Guinea, India, Liberia, Madagascar, Mozambique, Nepal and United Republic of Tanzania. Among this group, some major endemic countries (notably Brazil and India) are at risk of missing the target even by the end of 2005.

3.1 Major achievements

- By the beginning of 2003, more than 12 million cases had been cured.
- The number of countries showing prevalence rates above one per 10 000 population has been reduced from 122 in 1985 to 12 at the beginning of 2003.
- There is considerable reduction in uncovered areas, including those that are difficult to access or contain refugee populations, though this remains problematic.

[1] Invited but unable to attend

[2] *The final push towards elimination of leprosy: strategic plan 2000-2005*, WHO/CDS/CPE/2000.1, takes into consideration that the elimination target at the global level has been attained and in the next phase - "Elimination of leprosy as a public health problem is defined as reduction of the leprosy prevalence at a given point in time to a level below one case per 10 000 population at the national level."

- The gender imbalance existing in new case detection has decreased significantly.
- An increasing number of countries are requesting WHO for a free supply of MDT drugs.
- It is felt that the successes achieved in averting stigma, physical disabilities and socioeconomic burden, thanks to the implementation of the leprosy elimination strategy, are remarkable and should be better documented.

3.2 Major challenges

This first phase of elimination has been relatively straightforward as its main thrust focused on massive increase in geographical coverage of MDT, increased community awareness of the disease, and global advocacy.

However this first phase is best seen as a process of laying the foundation for the next, more difficult, phase in the elimination process, where we need to address the many structural and institutional constraints faced by those countries and those regions where the disease still survives as a major public health problem.

How best to implement this second phase, keeping in mind that our efforts over the next few years, in terms of integrating and sustaining leprosy control activities, must be robust enough to sustain the achievements? On the one hand, there are countries such as Angola, Liberia, Madagascar, Mozambique and Nepal that are facing severe economic and political challenges. These problems are hampering the implementation process and limiting access to MDT services in large parts of the country.

On the other hand, there are countries such as Brazil and India, which have adequate human and financial resources to make more rapid progress but which are lagging far behind. One of the most crucial issues still to be fully addressed is the continued presence of the highly vertical and centralized management structures, composed of specialized staff who are increasingly becoming an obstacle to the process of decentralization and integration. In addition, there is considerable reluctance to use a public health approach to deal with the problem in some major endemic countries, despite the fact that most of the endemic countries that have reached the elimination target managed to apply the strategy successfully, even with limited human and financial resources.

3.3 Role of WHO in the elimination process

WHO continues to work intensively with ministries of health, national programmes and nongovernmental organizations (NGOs) to make sure that the diagnosis and treatment of leprosy become an integral part of the national primary health care system.

Despite the formidable challenges that still remain, the basic groundwork for integration has now been completed in most major endemic countries. In this effort, giving ownership to local authorities has been an essential part of the integration process. For any endemic country, the final responsibility for eliminating leprosy - and for the health of its citizens in general – must remain with the government. WHO’s role is to facilitate this development process in terms of funding, technical advice, MDT drug supply and logistics, and global advocacy, but with the long-term view that the countries and the affected communities will "own" and sustain the elimination programme. During the transition period, WHO will continue with the process of developing a phasing-out strategy to ensure that countries continue to receive support for the most essential activities and that the achievements are sustained.

4. REPORT ON SCIENTIFIC WORKING GROUP ON LEPROSY

The TDR Scientific Working Group on Leprosy met at WHO headquarters, Geneva, in November 2002, to review the status of ongoing research activities in leprosy and develop a plan for future activities based on the needs of the elimination programme.

4.1 Ongoing global research efforts

Research on epidemiology of leprosy is limited by the problems associated with a low-incidence disease, the long incubation time and the lack of relevant tools. Serological tests for antibodies to *Mycobacterium leprae* PGL1 have been extensively characterized in endemic settings. Rapid simple assays are being evaluated in the field. Attempts are under way to identify antigens suitable for use as improved skin test reagents. These are undergoing initial evaluation in Brazil and Nepal. Recombinant proteins and synthetic peptides are also being investigated as potentially specific antigens in blood-based tests to measure T-cell responses to *M. leprae* as an indicator of infection.

Efforts are under way in a few laboratories to identify genetic polymorphism as the basis for development of strain–typing systems for *M. leprae*. Variations in short tandem repeat loci appear particularly promising.

A range of research efforts addressing nerve damage is currently being undertaken. These have been largely uncoordinated in the past but recent developments have led to more coordinated efforts. Work is in progress in basic sciences studying the mechanisms of neurotropism and the pathogenesis of nerve damage. A number of epidemiological studies have provided an important understanding of the risk factors for nerve function impairment and reactions. Several clinical trials of interventions for prevention and treatment of reactions, based on new regimens and new drugs, are nearing completion in Bangladesh, India and Nepal.

4.2 Corresponding research opportunities

The availability of *M. leprae* and other mycobacterial genome sequences provides important opportunities for identification of novel *M. leprae*-specific antigens that can be used for development of improved tests for infection. Sequence information is also central to prospects for development of molecular epidemiology approaches for leprosy. Leprosy research is also well placed to benefit from the rapid advances in post-genome technologies such as microarrays and bioinformatics.

Research on transmission is particularly timely given the current epidemiological situation, with MDT reducing the prevalence and the rate of new case detection showing a confusing trend of stable or increasing levels.

The genome project provides a specific research opportunity to explore neurotropism in leprosy. New Schwann cell models of *M. leprae* infection provide opportunities to investigate basic mechanism(s) of nerve damage in leprosy. New therapeutic opportunities are available based on a new generation of immunoregulatory drugs and TNF-α inhibitors. The development of standardized outcome measures, as a result of recent clinical trials for both nerve function and reactions, provide opportunities for new clinical studies.

4.3 Transmission

To sustain current successes and to approach the goal of eradication of leprosy, there is a need to identify new intervention strategies that complement MDT by targeting the reduction of transmission.

4.4 Nerve damage

Although MDT has had a dramatic impact on global prevalence, there are still two to three million people with deformities worldwide. In addition, in many parts of the world, its impact on rates of detection of new cases is unclear. Although a limited number of new cases will continue to occur in the coming years, these new cases will remain at risk of developing nerve impairment. Thus detecting, managing and understanding the mechanisms involved in nerve damage remain a high priority. Trials of prophylaxis and treatment of nerve damage have not provided optimal approaches for the prevention and management of nerve impairment. Therefore a combination of clinical and epidemiological research studies are required for the identification of risk factors, management, and prevention of nerve damage.

4.5 Research to improve integration

In most leprosy-endemic countries, leprosy control activities have been integrated into the general health services or are in the process of being integrated.

Major advantages of integration are increased accessibility to diagnosis and treatment, and decreased stigma attached to the disease, with increased levels of sustainability and cost-effectiveness. Regimens that shorten the duration of treatment and that are uniform for all patients will considerably simplify the administration of treatment by the general health services.

5. INTEGRATED DISEASE SURVEILLANCE

The use of an integrated health information system for collecting and collating data on leprosy is important for long-term, sustainable surveillance. Efforts are required to improve the quality as well as the coverage of the minimum data within such information systems. The minimum data requirement is the absolute number of new cases detected.

6. NEW INITIATIVE ON DEVELOPMENT OF DIAGNOSTIC TOOLS FOR LEPROSY

The completion of the entire genome sequence of *Mycobacterium leprae* represents a major landmark in the history of leprosy and opens new vistas for disease control. Unlike all other mycobacteria that have been characterized, including *M. tuberculosis, M. leprae* has undergone reductive evolution, losing many genes and biological activities. Its genome appears to encode a mere 1605 proteins and this is borne out by the findings of proteomic analysis which detected <500 protein spots. This is in stark contrast to *M. tuberculosis* and the environmental saprophyte, *M. smegmatis*, which are predicted to produce 4000 and 7000 proteins, respectively. Furthermore, bioinformatic analysis indicates that ~130 proteins, which are predicted in *M. leprae*, have no counterparts in other sequenced mycobacteria and may therefore be good candidates for the development of a diagnostic kit for detecting infection.

The aim of this project is to use a post-genomic approach to produce peptides, based on these and other candidates, such as surface-exposed or secreted proteins, and to determine experimentally whether such peptides do indeed contain T-cell epitopes. Thanks to improvements in T-cell epitope prediction algorithms, it is now possible to screen protein

sequences for peptides likely to correspond to epitopes recognised by CD4 and CD8 T-cells. These cells are important mediators of immunity to mycobacterial infection and their activity is the basis of the current delayed–type hypersensitivity skin test, employing partially purified protein derivative (PPD, tuberculin), which is used to detect exposure to *M. tuberculosis* or immunization by *M. bovis* BCG.

The intention is to synthesize 400 peptides, of 18–20 amino acids length, which have been identified as described above and shown to be absent (or of very different sequence) from other microorganisms. These will then be screened for T-cell reactivity using a whole blood interferon-gamma (IFN-γ) assay, as this cytokine is produced in a specific manner by T-cells that have previously been exposed to the corresponding antigen either in the course of the development of immunity or during disease. Experience from the field of tuberculosis shows that there are temporal differences in IFN-γ production: T-cells from individuals with the disease generally react within 24 hours, whereas those from healthy, immunized individuals require more than four days to do so because they are present only in low levels as memory cells that expand their population size only on exposure to the antigen.

Peripheral blood samples (6 ml) will be taken from consenting individuals using sterile disposable syringes and needles and transferred to the mycobacterial laboratory. The population to be sampled will include previously diagnosed leprosy patients and healthy individuals from both endemic and non-endemic countries. Pools of peptides (100 x 4; 10 μg/ml)) will be incubated with 50–μl aliquots of blood and incubated at 37 °C for 24 or 96 hours, and levels of IFN-γ determined by ELISA using commercially available kits. Those pools showing specific production of high levels of IFN-γ will be reanalysed and deconvoluted to identify individual peptides by retesting separately. Ultimately, pools of strongly reactive peptides will be formed and tested afresh to establish whether this leads to increased sensitivity. Testing will then be repeated with peripheral blood from lepromatous, borderline and tuberculoid leprosy to establish comparative sensitivity and specificity.

The first phase of development involves invasive methods that are unavoidable. Only in this way can large–scale screening of the peptides be undertaken. The later use of pools of peptides, that are specific and reactive is to be encouraged as this will allow possible differences in HLA type between individuals of different genetic and ethnic background to be overcome. This should ensure that the subsequent non-invasive test stands the highest chance of performing successfully, irrespective of the setting and ethnicity of the population. We expect to develop a transdermal test for infection employing an adhesive patch impregnated with the peptide pool, stabilizers and permeabilizing agents. Obviously, much work remains to be performed to establish the optimal time of exposure of skin to the patch and to correlate the size of the resultant induration with the clinical spectrum and immune status. It is very likely that this can be achieved within a period of four to five years if sufficient and sustained funding is made available.

7. CHALLENGES WITH CASE DETECTION AND ITS VALIDATION

7.1 New case detection

The issue of stable, or even increasing, detection in some countries or areas is a major concern and calls for in–depth discussion and analysis. Most of the new cases detected each year are in fact people who developed the overt disease several years earlier, but remained undetected for various reasons, including poor access to leprosy services and ignorance of the availability of a cure. Only a small percentage of newly-detected cases are true incident cases, i.e. experiencing

the onset of the disease within the last year. However, because of the lack of effective tools it is impossible to quantify the contribution of incidence to the annual new case load.

The reasons for the continued high detection rates in these countries are varied, but the most important are the limited geographical coverage of MDT services and therefore the poor access to leprosy diagnosis and treatment. A major operational problem is that leprosy diagnosis and treatment remain highly centralized, often conducted only by specialized staff. In addition, the guidelines followed in some countries are very rigid and complex. Although many policy decisions have been taken by countries to address these problems, their implementation is slow and the impact will not be perceptible for several years. This in part explains the substantial hidden caseload that still remains and serves as a reservoir of infection, spreading the disease in communities. Other reasons include the limited community awareness of the availability of free and effective treatment, and prejudice. These often lead to tragic consequences such as late diagnosis, high disability rates and low cure rates. An intense fear of leprosy still persists, though to a much lesser extent, and at times this leads to stigmatization of affected persons and their families.

In addition, some countries facing civil conflicts and economic turmoil have experienced severe physical damage to their health infrastructure, affecting all developmental projects and limiting leprosy control activities.

7.2 Validation

The elimination of leprosy, although defined as a reduction of prevalence below a particular level, depends to a large extent on a reduction of the occurrence of new cases. While a small number of countries show a downward trend in annual case detection, others show a steady or upward trend.

As attaining leprosy elimination depends very much on having reliable information on case detection, it is important to validate the case detection figures both through a review of registers as well assessment of the patients themselves. Programme-wide validation is most desirable but not always possible. However, in practical terms it is possible to get an insight into the situation through the validation of information on case detection, at least on a sample basis. While validation of wrong or over-diagnosis by the checking of records and patients is relatively easy to carry out, the validation of missing cases or under-diagnosis is not, as it involves the examination of large numbers of community members.

Wrong or over-diagnosis can be validated through sample checks of recently diagnosed cases applying standard procedures. During such checks, it should be possible to have a higher level of specificity of diagnosis including the collection of information on nerve damage, skin smears, and a detailed clinical picture.

The expected outcome of any validation exercise on case detection is to obtain a clearer understanding of the true situation of disease occurrence in any given area, and to sensitize health workers to possible problems of over- and under-detection so that they can perform more effectively in the future. As leprosy progresses towards being a low-prevalence disease, it is important to find tools and procedures to maintain a high level of specificity for confirming the diagnosis of a case of leprosy.

8. NEW CASE DETECTION AND ITS TRENDS

8.1 Experiences from Myanmar

The Myanmar programme effectively used the theme of the second International Conference on Leprosy Elimination, "Reaching every patient in every village", to intensify its case detection activities and expand the leprosy elimination programme to every corner of the country. The main elements of the strategy included: a) a capacity-building element in training programmes for all health staff to diagnose and treat leprosy; b) intensifying case detection through special and routine activities; c) improving geographical coverage and accessibility to treatment; d) improving and strengthening integrated services; and e) using appropriate Information, Education and Communication (IEC) techniques for improving community awareness and participation.

This Campaign approach resulted in a steep rise in case detection during the period from 1996 to 2001, reaching above 60 per 100 000 in 1999, followed by a decline to below 15 per 100 000 in 2002. As predicted, during the early phase special activities like LECs and SAPELs contributed a major share of the annual case detection, while at the same time strengthening the routine activities. During the later phase, the routine activities improved and contributed a larger proportion of new cases detected than the special activities. The special activities helped in expanding the programme coverage, detecting hidden cases and strengthening the integrated activities, and finally succeeded in achieving and sustaining the elimination goal set by the national programme. The evaluation of the intensified case detection activities during this period showed that the proportion of child cases and new cases with disabilities decreased over the period. In addition, the impact of the IEC activities resulted in more and more cases being detected within one year of the onset of the disease. On the negative side, it was evident that up to 20% new cases detected by the special activities were either wrongly diagnosed as leprosy or were old cured cases re-registered as new cases of leprosy. The programme plans to continue to strengthen routine case detection activities through IEC for the local communities and capacity building of general health staff in order to sustain the achievements made so far, and to work towards achieving elimination at subnational levels.

9. LEPROSY ELIMINATION CAMPAIGNS TO CONTINUE AS FOCUSED ACTIVITY

LECs are useful for promoting integration, changing the negative image of leprosy, training/motivating health staff, enlisting political commitment and promoting the participation of communities and local NGOs in elimination activities. New case detection rates have consistently shown declining trends when LECs have been repeated in the same area. The challenge will be to maintain an effective information, education and communication (IEC) strategy to promote self-reporting for diagnosis and treatment at the nearest health facility. There is no role for maintaining outdated active surveys which are costly, unreliable and more importantly perpetuate the negative image of leprosy in the community. Therefore, though LECs are needed in some countries, they should be focused on selected areas and use carefully identified LEC components.

10. ISSUES RELATED TO THE UNIFORM MDT (U–MDT) STUDY

The concept of using the MB MDT regimen for six months as a uniform regimen for all categories of leprosy patients (MB and PB) has raised several interesting questions, and has been a subject of active debate for quite some time. The basic protocol for the study was made

available through the WHO/TDR Web site. In addition to the basic protocol, a detailed background document was prepared and this background document was extensively reviewed by the Technical Advisory Group. However, the background document was not widely available and therefore some scientists and research workers have raised a number of doubts and questions. These were extensively discussed by members of TAG. Some of these are:

- ***Why can't a Randomized Controlled Trial approach be considered?***

Implementation of the project is to be undertaken for all cases of leprosy. PB leprosy patients constitute the substantial majority of these cases and for them the question of interest is only the addition of clofazimine. The main issue to be addressed for this group is one of acceptability and can be tackled in an open study design.

With respect to the MB cases, the risk of possible inadequate treatment might exist for about 2% of all newly diagnosed leprosy cases. Even in this group it is not certain whether the observed high relapse rates in limited studies are the result of reactivation or reinfection. In the event of relapse, the event can easily be managed by administering an additional course of U–MDT. If a randomized controlled trial needs to be conducted at all, it could be justified in this small fraction of highly bacteriolgically positive patients. It will need a control group of patients receiving 12 months MB MDT. The sample size calculations will have to be based on the principle of equivalence and the numbers will be enormously large. Such a trial is not a practical proposition. It needs to be stressed that the practice of routinely taking skin smears has been discontinued for several years. Hence it is not possible even to identify the cases who possibly could be at a higher risk of relapse.

- ***Goal of the study***

The main objective of this proposal is to demonstrate the usefulness of a single short treatment regimen for all patients of leprosy. This operational goal is not an unscientific one, and implementation has major operational and cost benefits.

- ***Relapse rate of 5% over five years***

There is no consistent information on relapses in MB patients. Some studies report relapse rates as high as 4% or more and others show the risk to be negligible even in cases with high initial Bacteriological Index (BI). There are no clear answers to this complex question but reinfection could be an explanation. Thus, relapse is the parameter that could be considered dependable in field practice. Since new lesions occur on account of both disease activity and reactions, the specificity of new lesions as markers of relapse will remain doubtful. However, this approach of considering an acceptable level of 5% over a period of five years as failures, based on "relapses", would take care of the patients' interest and is therefore ethically acceptable.

- ***Clofazimine for PB cases***

For PB leprosy, WHO recommends six–months' MDT, consisting of monthly pulse rifampicin and daily dapsone. Persisting skin lesions, even after completion of effective six–months' PB MDT therapy is a major challenge to the implementation of MDT. Relapses and reactions in patients on PB MDT is an area of concern, though the estimates are highly variable in different studies.

Information on relapses in PB leprosy is variable. In different studies the definitions adopted for relapse differ considerably and comparisons become difficult. Rates in the published studies vary from 0.12 to 3.0 or more per 100 patient–years. Based on an extended post-MDT questionnaire survey conducted by WHO, covering more than 50 000 PB leprosy patients, the relapse rate was 1.07% in 9 years after stopping MDT. In a study from India based on 14 227 patients, the observed relapse rate for the first year was 0.33% and it was similar in those who received six–months' PB MDT and those who received it for a longer duration. In a study from Ethiopia, 34 relapses were seen in 3065 PB patients after an average period of 6.1 years since stopping treatment. Out of these 34, in only 16 was there definitive evidence for relapse. In a review article, the expected cumulative probability for relapses in PB leprosy following WHO–recommended MDT was estimated as approaching 5% over a 10–year period. Since in several of the published studies, data on leprosy are obtained through routinely collected data from programme conditions, there is a possibility that the estimates of relapse may not be realistic. It is also possible that details of the regularity of treatment may not have been carefully considered before the relapse rates were calculated.

In a randomized controlled clinical trial conducted in India, the efficacy of PB MDT plus daily clofazimine was compared with PB MDT. It was seen that the proportion of persisting active skin patches was considerably reduced by the addition of clofazimine. As compared with 16% active persisting skin lesions in the standard PB MDT arm, the observed proportion of such lesions in the study regimen was only 7.5% at the end of 6 months' treatment. This difference was statistically significant. In the next 6 months of observation, activity reduced by 80% in the study group compared with only 30% in the control group of patients. This trial gives further indications that both early and late reactions and relapses could be much reduced through the U–MDT approach. Investigators noticed further that clofazimine was well accepted by the patients and that pigmentation was minimal, and rapidly disappeared after stopping treatment.

- ***Informed consent***

Minimum essential information was given in the original consent form enclosed with the proposal. It will be expanded and modified to suit different cultural, social and regional backgrounds.

- ***Recruitment of cases***

All new cases will be provided with detailed information about the uniform drug regimen, its advantages and limitations. Only patients willing to join the U–MDT study (having given their informed consent) will be recruited for the study.

- ***Training***

The study will be conducted in areas or programmes having reasonably well organized leprosy control services with adequately trained staff. This will be judged by field visits by WHO monitoring teams. Orientation workshops will be organized by individual study sites as well as by the coordinating agency for the study.

- ***Reduced duration of MDT***

It is possible that the duration of the current MDT regimen for MB leprosy could be shortened to six months without increasing the risk of rifampicin resistance developing.

Available information on bactericidal activities of various drugs and combinations is given in the background document.

- ***Sites for the trial***

The study sites will have an opportunity for institutional and human resource strengthening. The proposal will also have a training and reorientation component. Trial monitors would be selected on the basis of their expertise and experience.

- ***Other issues***

Definitions for relapse and reactions are given in the protocol, but it is often difficult to distinguish them. That is why a level of 5% significance is set for relapse rates. The role of standardized independent monitors for the trial becomes important.

Effectiveness will be measured in terms of the number of patients accepting the U–MDT regimen, the number of relapses, safety and compliance.

11. FREE MDT SUPPLY

WHO has supplied MDT to all endemic countries since 1995, and now provides treatment for close to 100% of all known patients worldwide. WHO's ability to plan for, procure and supply such large quantities of MDT, and at the same time be able to respond quickly to small emergency requests, has largely been the result of a close collaborative effort between governments, WHO and Novartis. Global buffer stocks of MDT are held at the supplier's factory at their own expense to meet emergency requests, and in 2003 will be equivalent to around 30% of the total global annual demand.

A full scale redesign of the blisters and their packaging, aimed at improving resistance to environmental heat, moisture and physical damage in the field, was implemented in 2002. This also made the treatment more "patient–friendly" – an important factor in treating a disease that carries with it the stigma of the past. A new pack of six blisters has been introduced, corresponding to a full course of treatment for PB patients, while two packs would accommodate the full course for MB patients. These packs perfectly complement the current WHO initiative to encourage treatment within the community – "accompanied MDT" – which will provide patients with an alternative choice to the monthly "supervised" doses usually insisted upon by centralized delivery systems, often at the cost of low patient compliance. The boxes as now presented contain patients' information leaflets in four languages (English, French, Brazilian Portuguese and Hindi).

TAG strongly recommends that WHO should continue to supply high–quality MDT drugs, free of charge to all countries in need.

12. ISSUES RELATED TO ACCOMPANIED MDT (A-MDT)

MDT has been proved to be effective and safe and there was a growing feeling that monthly supervision is not really necessary any longer, as it hampers integration and is not user-friendly to mobile populations or patients living in remote areas and/or areas affected by civil strife. This concept was applied by WHO during the SAPEL projects, which specifically dealt with populations/communities living in difficult–to–access areas or in conditions where regular contact with health services was not possible. The experiences from about 80 SAPEL projects

carried out all over the world suggested that patients, their friends, family and community leaders can play an important role in ensuring that the full course of treatment is taken, provided that all participants are well informed about the disease, its treatment , and when and where to report in the event of complications.

The members agreed that the use of A–MDT would give better access to MDT for all patients in general and specifically for those who are unable to visit the health centre regularly for various reasons. Contrary to fears expressed, A-MDT will ensure better supervision of the entire treatment, as the accompanying person would ensure that the monthly and daily medications are swallowed regularly. In case of complications, the patient and the accompanying person are made aware that the health facilities can be visited anytime. Patients choosing A-MDT as their treatment option and the person accompanying them should be fully informed about the disease and treatment, including the importance of reporting promptly to the health centre in case of complications, and at the end of treatment. TAG recommends that WHO prepares and distributes technical guidelines for the use of A-MDT and that countries should be encouraged to document their experiences of its use under field conditions.

13. UPDATING LEPROSY REGISTERS

The experiences from several endemic countries clearly indicate that, in spite of significant improvements in practices related to case registration and case management, some serious drawbacks still exist. Many exercises carried out by programmes to improve registration practices and update registers in Cameroon, Chad, Côte d'Ivoire, India, Madagascar, Mozambique, Myanmar, Nepal, Niger and United Republic of Tanzania have indicated that, at any given point in time, between 40% and 75% of patients shown on the treatment registers should not have been there. Such exercises also helped in making the field staff aware of the importance of updating registers, making the correct diagnosis and following the national guidelines on case definitions and treatment durations.

There are several reasons why patients are kept on the registers even after completion of their required course of MDT regimen. In some cases this is related to lack of supervision or non-adherence to national treatment guidelines and in others it is intentional, to show an inflated disease burden in the area.

Such practices have clearly undermined the achievements of the programme and made a situation analysis difficult. The most practical indicator that something is going wrong and needs corrective action is the prevalence/detection ratio (P/D ratio). In theory, the number of cases remaining on the registers at the end of the year (point prevalence) should be less than the number of newly detected cases during the year. In other words, the P/D ratio should be less than 1.0, and may be as low as 0.5. Most programme managers feel that as overall prevalence is decreasing the problem is becoming acute in some areas and projects. Some countries that have already reached elimination level, or are very close to reaching it, may find that poor registration practices and the failure to update registers can result in an inflated prevalence rate. Every programme will need to monitor this carefully and provide national guidelines to make updating registers a regular exercise before finalizing the annual statistics.

14. PHASING-OUT STRATEGY: HANDING OVER

GThe WHO Strategic Plan 2000–2005,[3] which is endorsed by all endemic countries, has clearly described the time frame for achieving elimination in all the remaining countries and the steps in developing a phasing-out strategy.

The most important component of the strategy is to ensure that MDT services[4] are available and accessible to the affected community at the nearest health facility. The complete integration of MDT services within the existing general health services is crucial to achieve and sustain elimination. In addition, the national programmes need to dismantle the specialised leprosy control services and make appropriate reallocation of their staff. Several endemic countries have already successfully integrated their leprosy control services, mainly because of the urgent need to expand MDT coverage. However, in some countries with large specialised elements the progress is slow and patchy. These countries may require assistance in carrying out structural adjustments to accelerate the integration process. Some elements of the specialized structures will need to be kept at the central level or at an intermediate level as referral facilities to provide technical assistance, monitoring, research, and training activities.

The countries that have already achieved the elimination target at the national level have prepared their plans to focus attention on subnational levels in order to reach the target at state/district/provincial level. In addition, programmes should proactively identify uncovered areas and populations for intensified activities.

The collection and analysis of information on leprosy remain too complicated for the basic health workers. Programmes should now discontinue routinely collecting extensive and complex information that is rarely or never used. The information collected should be kept to a minimum and should be consistent with the reporting format for other communicable diseases handled by the general health workers. The use of an integrated health information system for collecting and collating data on leprosy is important for the long-term, sustainable surveillance of leprosy. The minimum data required for monitoring leprosy at any level is the absolute number of new cases detected during a defined period in time.

The concept of certification or validation at any level is more appropriate for the eradication of a disease. The development of tools and approaches for such an exercise is technically relevant only for a disease eradication strategy. The validation or certification of leprosy elimination at a point of time is a difficult and time-consuming exercise that may not be a relevant or cost-effective public health measure. However, the need and approaches for assessing progress with the elimination of leprosy at any level are important for the programmes before, during, and after the elimination goal has been achieved. In this regard, leprosy elimination monitoring (LEM) exercises have proved to be an effective method of independently assessing leprosy elimination activities, including the evaluation of all the elements of integration. It is important that national programmes document their achievements in order to share experiences and motivate other public health programmes.

Progress made during the past decade is largely due to the commitment and determination of the national governments and their partners at the country level. The “ownership” of the programme has gradually shifted from charitable organizations and NGOs to the national health

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[3] The final push towards elimination of leprosy: strategic plan 2000-2005. WHO/CDS/CPE/CEE/2000.1

[4] MDT services include diagnosis, treatment with MDT, patient and family counselling, community education and referral for complications.

services. This has resulted in programmes "owning" their plans of action and adjusting their strategies to suit local realities. National and international NGOs will now have a greater role to play in handing over the leprosy control activities to national health services and in focusing on other supportive activities.

The role of WHO will change as countries take full ownership of their programmes and implement the integration strategy to achieve and sustain elimination at all levels. WHO plans to continue assisting countries with a free MDT supply, technical guidelines, and surveillance, and, where necessary, in developing strategies for sustaining leprosy control activities within the general health services. Although it is likely that some major countries, such as Brazil and India, will miss the 2005 target date for achieving elimination at the national level, WHO does not propose to change the definition of elimination or give any new target date for elimination.

15. REVIEW OF U-MDT PROPOSALS

The protocol for the U-MDT study and call for proposals were made available globally after the fourth meeting of TAG. In response to this, WHO received nine proposals from five countries. In addition, one proposal was submitted to coordinate several proposals from one country. TAG members approved proposals from four centres which met all the selection criteria. TAG also approved the proposal from one of the national institutions to coordinate activities related to the multicentre study on U-MDT for all the approved participating centres.

16. WHO GUIDELINES FOR THE MANAGEMENT OF SEVERE ERYTHEMA NODOSUM LEPROSUM (ENL) REACTION

16.1 General principles

1. Severe ENL reaction is often recurrent and chronic, and may vary in its presentation.
2. The management of severe ENL is best undertaken by physician at a referral centre.
3. The dose and duration of anti-reaction drugs used may be adjusted by the physician according to the individual patient's needs.

16.2 Definition

Severe ENL reactions include:

- numerous ENL nodules with high fever;
- ENL nodules and neuritis;
- ulcerating and pustular ENL;
- recurrent episodes of ENL;
- involvement of other organs (e.g. eyes, testes, lymph nodes, and joints).

16.3 Management with corticosteroids

- If still on antileprosy treatment, continue the standard course with MDT.
- Use adequate doses of analgesics to control fever and pain.
- Use standard course of prednisolone in daily dosage not exceeding 1 mg/kg body weight. Total duration 12 weeks.

16.4 Management with clofazimine and corticosteroids

This is indicated in cases with severe ENL who are not responding satisfactorily to treatment with corticosteroids or for whom the risk of toxicity with corticosteroids is high.

- If still on antileprosy treatment, continue the standard course with MDT.
- Use adequate doses of analgesics to control fever and pain.
- Use standard course of prednisolone in daily dosage not exceeding 1 mg/kg body weight.
- Start clofazimine 100 mg three times a day for maximum of 12 weeks.
- Complete the standard course of prednisolone. Continue clofazimine as below.
- Taper the dose of clofazimine to 100 mg twice a day for 12 weeks and then 100 mg once a day for 12–24 weeks.

16.5 Management with clofazimine alone

This is indicated in cases with severe ENL where use of corticosteroids is contraindicated.

- If still on antileprosy treatment, continue the standard course with MDT.
- Use adequate doses of analgesics to control fever and pain.
- Start clofazimine 100 mg three times a day for maximum of 12 weeks
- Taper the dose of clofazimine to 100 mg twice a day for 12 weeks and then 100 mg once a day for 12–24 weeks.

Note:

- If the MDT treatment is already completed the management of ENL should follow the guidelines. There is no need to restart MDT.
- The total duration of a standard course of corticosteroids (prednisolone) is 12 weeks.
- The total duration of treatment with high dosage clofazimine should not exceed 12 months. It takes about 4–6 weeks for clofazimine to take full effect in controlling ENL.
- Another drug claimed to be useful in ENL is pentoxifylline, alone or in combination with clofazimine and/or prednisolone.
- Because of the well known teratogenic side–effects, WHO does not support use of thalidomide for the management of ENL in leprosy.

17. CONCLUSIONS AND RECOMMENDATIONS

1. TAG acknowledges that the majority of countries where leprosy was considered to be a public health problem have now attained the goal of elimination[5] at the national level. However, an analysis of the current global leprosy situation indicates that a few major endemic countries (notably Brazil and India) are likely to miss the goal of elimination at the national level by the end of 2005. TAG recommends that WHO should play a key role in reviewing their plans of action for the coming years and, where necessary, assisting in developing more focused plans in order to reach elimination as early as possible.

2. TAG members expressed their satisfaction that many countries have reached the elimination goal, in spite of many constraints, by using flexible approaches that are both innovative and cost-effective. The experiences from such countries will motivate other disease

[5] The elimination of leprosy as a public health problem is defined as the reduction of the leprosy prevalence at a given point in time to a level below one case per 10 000 population, at the national level.

control programmes within the countries themselves and also national programmes in other countries that are currently lagging behind. TAG urges WHO to encourage and guide countries in documenting their experiences and the lessons learnt for wider distribution.

3. TAG notes that most of the countries that have already attained the elimination goal at national level, and have developed plans and strategies for sustaining leprosy control and reaching the elimination goal at subnational levels. WHO should, where needed, assist countries in implementing such strategies.

4. Concerned with the stable and high new case-detection trends observed in some major endemic countries, TAG recommends that WHO should develop protocols to undertake studies for analysing and validating case detection, as reported by routine information systems. Such studies should be undertaken as soon as possible.

5. In keeping with the urgent need in the field, and the progress made following complete decoding of the genome map of *Mycobacterium leprae*, TAG recommends that WHO pursue the development of tests for leprosy diagnosis within the next two years. It also recommended that all efforts should be made to ensure that such tests are available for use in the field programmes within the next 5 years.

6. TAG restates its recommendation that leprosy elimination campaigns (LECs) are a useful approach to accelerate elimination activities in specific endemic areas. However, LECs should now be focused only on high endemic pockets, underserved communities and previously uncovered areas.

7. TAG recommends that all programmes should ensure that treatment registers are periodically updated and that good registration practices and guidelines are followed uniformly.

8. TAG reaffirms that the use of Accompanied-MDT would give better access to MDT for patients in general and specifically for those who are unable to visit the health centre regularly for various reasons. Patients choosing A-MDT as their treatment option and the person accompanying them should be fully informed about the disease and treatment, including the importance of reporting promptly to the health centre in case of complications, and at the end of treatment. TAG strongly recommends that WHO prepares and distributes technical guidelines for the use of A-MDT and that countries document their experiences of its use under field conditions.

9. TAG strongly recommends that WHO should continue to supply high–quality MDT drugs, free of charge to all countries in need, in order to achieve and sustain elimination.

10. TAG reiterates that the use of an integrated health information system for collating data on leprosy is important for the long-term, sustainable surveillance of leprosy. The minimum data requirement for monitoring leprosy at any level is the absolute number of new cases detected during a defined period in time.

11. TAG considers that validation or certification of leprosy elimination at a point of time is a very difficult and time-consuming exercise that may not be relevant or cost-effective. The development of tools and approaches is technically relevant only for a disease eradication strategy. However, the need and approaches for assessing progress with elimination of leprosy at any level are important for the programmes before, during, and after the elimination goal has been achieved. In this regard, leprosy elimination monitoring (LEM) continues to be an effective

method of independently assessing leprosy elimination activities. TAG encourages further efforts to develop suitable methods for this purpose.

12. Poverty alleviation measures are likely to have an impact on leprosy transmission. TAG recommends that WHO collect information on poverty alleviation measures taken in countries with a high burden of leprosy and disseminate this information to TAG members for discussion during the next TAG meeting.

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Annex 1

WHO Technical Advisory Group on Elimination of Leprosy (TAG)
Yangon, 9 and 10 February 2003

AGENDA

Sunday, 9 February 2003

09:00–09:15	Opening *(Dr Daumerie)*
09:15–09:30	Chairperson's remarks *(Dr Becx-Bleumink)* Introduction of participants
09:30–10:00	Reports on third and fourth meetings of TAG *(Dr Becx-Bleumink)*
10:00–11:00	Global situation and remaining challenges *(Dr Daumerie)* Discussion
11:30–12:00	Report on Scientific Working Group on Leprosy *(Professor Smith and Dr Engers)*
12:00–13:00	New initiatives on diagnostic tools *(Professor Cole)* Discussion and recommendations
14:00–15:30	Challenges with detection trends and its validation *(Dr Noordeen)* Discussion
16:00–17:30	Challenges with detection trends: experiences from Myanmar *(Dr Kyaw Nyunt Sein)* Discussion and recommendations

Monday, 10 February 2003

09:00–09:45	Uniform MDT (U-MDT) *(Dr Gupte)* Discussion and recommendations
09:45–10:30	Accompanied MDT (A-MDT) *(Dr Awe)* Discussion and recommendations
11:00–12:30	The exit strategy: phasing out and handing over *(Dr Becx-Bleumink)* Discussion and recommendations
12:30–13:00	Conclusions and recommendations
14:00–17:30	Special session: for TAG members only Review of U-MDT research proposals. Review of draft guidelines for management of severe ENL.

Annex 2

WHO Technical Advisory Group on Elimination of Leprosy
Yangon, 9 and 10 February 2003

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