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

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