6.1 The WHO Leprosy unit

Overview

S.K. Noordeen

The World Health Organization was chiefly responsible for developing and promoting – and to an extent implementing – MDT. The WHO Leprosy unit played a key role in promoting acceptance of the recommendations of the 1981 Study Group by WHO regional structures, Member States, NGOs, donor agencies, and technical persons responsible for leprosy control. The Organization’s promotional efforts were carried out through global, regional, and national meetings and discussions. The support provided by WHO to countries through extrabudgetary funding, mainly from The Nippon Foundation, facilitated the process of implementing treatment with MDT greatly; significant support (including technical guidelines, training, logistics, and limited procurement of MDT drugs) was also provided to countries directly by international NGOs and other funding agencies. As long as countries had sufficient political commitment and reasonable health infrastructure, it was not difficult to mobilize funds for MDT drugs and related leprosy control activities. Implementation of MDT was also discussed in very positive terms at many of the scientific meetings held outside WHO, such as the International Leprosy Congresses. Member associations of ILEP were also able to increase MDT coverage in the projects they supported.

In terms of developments in different WHO regions, the situation in the Eastern Mediterranean and in the Western Pacific, where the leprosy problem was relatively limited and support from NGOs and donor agencies quite strong, were relatively favourable. The African region also received good support from NGOs, and in several African countries there was a downward trend in leprosy prevalence. In the region of the Americas, the problem was one of acceptance of MDT and its widespread application: until the early 1990s, implementation of MDT was somewhat limited in major countries such as Brazil.

The South-East Asia region had three-quarters of the global leprosy burden, with very high prevalence in many countries. Despite the relatively early introduction of MDT and significant reductions in prevalence, residual prevalence remained quite high.

Overall, it was possible by the end of the 1980s to implement MDT in all areas with good health development, political commitment, and donor support – yet more than half of all patients were still not receiving MDT. It therefore became necessary to vigorously promote political commitment to leprosy as well as to make the necessary resources available; this was made possible through adoption of the World Health Assembly resolution on elimination of leprosy in 1991 and the pledge of US$ 50 million for 5 years’ support to purchase MDT drugs.
made by the Nippon Foundation at the first International Conference on Leprosy Elimination (Hanoi, 1994). As a result of these two developments, without which it would have stagnated at around 50%, MDT coverage increased rapidly, reaching almost 100% by 1997 (see section 3.1).

From the technical point of view, WHO facilitated wider implementation of MDT through simplification of technical requirements and managerial capacity-building. The simplification of technical requirement included:
- classifying leprosy as MB and PB on clinical grounds without necessarily depending upon laboratory services as recommended by the WHO Study Group on Leprosy Chemotherapy in 1993;
- fixing the duration of MDT at 24 months in 1993 and reducing it to 12 months in 1997 on the basis of recommendations made by the seventh meeting of the WHO Expert Committee on Leprosy;
- introducing a single dose ROM treatment for single skin lesion leprosy, again on the recommendation of the seventh meeting of the Expert Committee;
- abandoning the requirement for active surveillance of patients after completion of treatment.

WHO also placed a major emphasis on training programme managers in leprosy control. Management workshops were organized in a number of countries in which managers were trained to plan, implement and evaluate leprosy control and elimination.

**Detailed account**

*H. Sansarricq*

**The decade that prepared the ground for the 1981 Study Group Meeting**

A series of important steps, many interrelated and some initiated directly by the WHO Leprosy unit, were taken over the 10-year period from 1972 that led up to the 1981 meeting of the WHO Study Group. Their importance, recalled below, can be better understood in the context of the situation in the late 1960s, which is briefly summarized.

**Difficulties with dapsone resistance (late 1960s)**

Although secondary resistance of *M. leprae* to dapsone was first demonstrated in 1964 (1), the WHO Expert Committee on Leprosy had concluded at its third meeting in 1966 that “the question of drug resistance to DDS is not an important one” (2). Indeed, dapsone resistance was not discussed as a specific topic at the fourth meeting of the Expert Committee in June 1970 (3). It was mentioned indirectly only twice, in relation to: (a) the fear that low doses of dapsone would favour the development of resistance, and (b) the possibility of demonstrating resistance by Shepard’s mouse footpad method.

In the late 1960s, LEP did not feel that dapsone resistance was a serious problem, possibly because of the long duration of dapsone monotherapy necessary before drug resistance could be observed and the low frequency of the phenomenon at that time. It is also likely that, for strategic reasons, LEP was unwilling to recognize the importance of dapsone resistance as long as there was no alternative to the dapsone monotherapy regimen.
In the area of research, however, LEP seemed more progressive. In June 1970, a WHO informal consultation on immunological problems in leprosy research, organized jointly by LEP and IMM (Immunology unit), was held in Geneva. The final report of the meeting (4) gave a good account of immunological aspects of leprosy at that time, yet LEP still had reservations in respect of some important advances in the understanding of leprosy, particularly the significance of the Ridley–Jopling classification – an essential tool for immunological research in leprosy.

Change in the perception of research problems in LEP

The meeting of investigators on immunological problems in leprosy research (5), held in New Delhi in 1972 and jointly organized by Dr Goodman, Chief, IMM, and Dr Bechelli, Chief, LEP, proved to be a turning point. During that meeting, the author – participating as the new head of LEP – had the opportunity to demonstrate clearly that the Leprosy unit was now receptive to advances in leprosy research and willing to take advantage of these for improving leprosy control methods, cooperating fully with the scientific community.

New developments

- Establishment of IMMLEP and TDR
  After the New Delhi meeting, Howard Goodman and the author were wholly convinced that they should work together to promote research on the immunology of leprosy. With this aim, IMM (rather than LEP, which still lacked the resources) recruited Tore Godal on a one-year consultancy (1973–1974) to draft the outline of a research plan. The first meeting of the IMMLEP project group was convened subsequently (4–8 November 1974) (6).

  At that time, there was general recognition of the need to actively develop research in the area of tropical diseases (see Introduction), and this was reflected, for example, in resolution WHA27.52, adopted on 23 May 1974 at the Twenty-seventh World Health Assembly (7). Although it was parasitic tropical diseases that were cited, the fact that the IMMLEP group was already set up allowed WHO to respond to the resolution by promptly establishing in November 1974 an overall plan for a programme for research and training in tropical diseases (8) – later to become the UNDP/World Bank/WHO Special programme for Research and Training in Tropical Diseases, TDR. Since this plan started with the IMMLEP model, leprosy was included in the list of TDR diseases from the outset, in addition to the five strictly parasitic diseases. Table 6.1 outlines the process that resulted in the establishment of IMMLEP and TDR during the years 1973–1976 and indicates the involvement of LEP in these steps as appropriate. It may be noted that certain components of TDR (e.g. THELEP) started work before the overall TDR machinery was set in motion.

  The launching by WHO of an important and innovative research programme, involving scientists of world repute and with adequate financial resources permitting for effective support of the selected projects, soon gave real strength and visibility to the leprosy programme, which would grow and develop with time – first through IMMLEP and subsequently through THELEP.

- Donations by Mr Sasakawa
  Following the establishment of IMMLEP and TDR, there was an important development in the form of a donation by Mr Ryochi Sasakawa – a grant of US$ 502 000 which was transferred to the WHO budget for leprosy in 1975. Previously, WHO was frequently able
to offer only advice and recommendations to leprosy-endemic countries, whose
governments would then have to seek funding for the implementation of that advice. With
this grant and other extrabudgetary funding that became available, WHO was able not
only to provide the appropriate advice but also to support financially its implementation.
As a consequence, government authorities and WHO officials at all levels – country
representatives, regional advisers, and headquarters leprosy staff - grew increasingly
confident and enthusiastic about the feasibility of controlling leprosy at the global level.
With the support provided directly by other voluntary agencies, it was now possible
adequately to cover the needs of practically all leprosy control projects.

Over the years, the support to leprosy control activities contributed to a general
improvement in and reorganisations of a number of national programmes and thus to the
sustainability of their activities. Its important long-term impact was in preparing the
ground for the implementation of future MDT activities. However, WHO was not yet in a
position to respond effectively to the current leprosy problem as control methods based on
dapsone monotherapy alone had not yet been improved.

➢ Establishment of THELEP

The purpose of TDR was to stimulate, coordinate, and support investigations of all aspects
of six selected tropical diseases. Apart from immunology, chemotherapy merited
immediate consideration – which is why a Scientific Working Group (SWG) on
Chemotherapy was set up for each of the six diseases. The first step in establishing the
THELEP SWG was a meeting of a few selected leprosy researchers in Geneva,
28–30 April 1976 (9), at which the following objectives of the THELEP programme were
identified:
– field studies on dapsone resistance (mainly dapsone resistance surveys);
– laboratory studies aiming at improving methods in chemotherapeutic investigations;
– clinical drug trials;
– development of new antileprosy drugs.

➢ The fifth meeting of the WHO Expert Committee on Leprosy (10)

With regard to the efforts of LEP to acknowledge the most recent advances in leprosy
research and stimulate further research on improving control methods, the establishment
of IMMLEP and THELEP provided an invaluable opportunity. While participating in the
TDR specialized research activities, LEP continued to be responsible for the definition
and adaptation of WHO technical policy for leprosy control, principally through meetings
of WHO Study Groups and the WHO Expert Committee on Leprosy. Taking account of
the advances made during the previous decade in the understanding of leprosy – including
those that had not been acknowledged by the fourth meeting of the Expert Committee in
1970 – LEP considered it timely to convene a fifth meeting of the Expert Committee in
October 1976.

The Committee acknowledged the existence of secondary dapsone resistance and of
microbial persistence. The possibility of primary dapsone resistance was also recognized,
although it had not yet been reported. At that time, “clinical experience of combined
therapy with rifampicin and clofazimine in combination with dapsone was too limited to
allow of decisions on optimum regimens for different forms of leprosy. Furthermore, there
was fear of toxicity and other complications” (11).
To prevent the emergence of secondary sulfone resistance, the Committee considered that “initial combined therapy should be given to newly diagnosed lepromatous and borderline cases”. For initial combined therapy it was proposed to add to dapsone in full dosage:

− either clofazimine, 100 mg daily or three times a week during the first 4–6 months of treatment, followed by dapsone alone;
− or rifampicin, 300–600 mg daily for a minimum of 2 weeks, followed by dapsone alone.

In dapsone-resistant cases, suggested treatment was 600 mg of rifampicin daily with 100 mg of clofazimine daily for 2–3 months, followed by clofazimine indefinitely. In a footnote, daily treatment with rifampicin was “strongly advocated … because of the known toxic effect of rifampicin when the drug is taken intermittently”.

The basic recommendations on combined regimens were based on sound scientific knowledge, but clinical experience was too limited to permit a decision on optimal regimens for different forms of the disease. The most significant difficulty was that “intermittent therapy could not be recommended at this stage” (12). In the few attempts that were made to implement these recommendations (only in India), the organization of supervised daily delivery sessions for rifampicin and clofazimine met insuperable difficulties. Thus, although the fifth meeting of the Expert Committee showed that the importance of dapsone resistance was now fully appreciated in WHO, its recommendations – while based on the available scientific knowledge – had virtually no impact on the leprosy problem.

The 1981 Study Group meeting

LEP recognized that the recommendations included in the report of the fifth meeting of the Expert Committee, published in 1977, did not respond to the needs of control programmes but fervently hoped that THELEP would find an appropriate solution. In 1979, there was particular hope that the MDT regimen of the THELEP protocol for field trials (13, 14) in lepromatous leprosy would meet LEP expectations for MB patients. However, it was soon realized that the need to carry out the protocol before recommendations for field use could be derived from the results would cause a long delay – and a rational alternative to the anarchic use of rifampicin was urgently needed. Thus, although it was decided to convene the Study Group on chemotherapy of leprosy for control programmes in 1981, recommendations were made for immediate field use of regimens proposed by the study group. The roles of THELEP and LEP in the development of the Study Group regimens are summarized in Table 6.2.

The role of THELEP

It is clear that the regimen recommended by the 1981 Study Group for MB patients – the most important conceptually – was not very different from that designed by THELEP in 1979 for its field trials (14). Clearly, the Study Group’s recommendation for MB patients was essentially the result of discussions that had been taking place since March 1979 within the THELEP SWG and Steering Committee. The changes incorporated during the Study Group sessions were also, to the best of the author’s recollection, the result of discussions between THELEP experts within the Study Group. The regimen for PB patients, proposed for discussion in the working paper by Vellut & Waters (12) and recommended by the Study Group, was also the result of previous THELEP discussions. Thus, the development of the 1981 Study Group regimens was essentially a product of THELEP work and discussions.
The role of LEP

The WHO meetings of experts – Expert Committees and Study Groups – generally recommended for implementation only therapeutic schemes that had already been shown to be effective and safe in controlled trials of acceptable methodology. Leprosy, however, posed greater problems in this regard than other microbial diseases since demonstrating the efficacy of any MDT regimen for MB patients required the observation of relapses in patients over several years following the completion of chemotherapy. The course of MDT administration itself had been fixed at 2 years in the THELEP protocol for MB MDT. It was clear that a different approach would have to be used if recommendations for immediate implementation were to be issued.

During the preparatory phase of the Study Group meeting, LEP could have tried to convince its senior management that the risks inherent in the growing anarchic use of rifampicin justified WHO’s designing MDT regimens which, in all likelihood, would be effective and safe and recommending them for immediate implementation. However, it was thought that such an approach would be refused, probably on the basis that experience with the monthly administration of rifampicin was too limited. It was also feared that any similar attempt by THELEP would have been judged to be outside its terms of reference, which were for research rather than control procedures.

Thus, convinced that the experimental THELEP regimen for MB patients, designed in 1979, was likely to respond to the needs, LEP decided to convene the 1981 Study Group in an effort to:

− obtain from THELEP researchers proposals for MDT regimens for MB and PB patients that were the most likely to be effective, safe, and practicable;

− have these regimens recommended for immediate implementation by a group of THELEP and leprosy control experts;

− have these recommendations for immediate implementation approved by WHO decision-makers and governing bodies (i.e. the Executive Board).

It seemed that the best way to have the expected recommendation approved by the WHO decision-making level for immediate implementation was to mention this requirement clearly but with great discretion. This is the reason for that essential point being deliberately omitted from the proposal for a Study Group meeting submitted to the decision-making level, and mentioned only briefly in both the working paper by Vellut & Waters (12) and the final report of the Study Group meeting (11).

Promoting the Study Group recommendations (1981–1985)

Once the Study Group recommendations were formulated, it became a top priority for LEP that they be implemented as accurately and as widely as possible – and the author was witness to just how actively and enthusiastically this new and complex goal was pursued. Clearly, the greater complexity of the new treatment procedures meant that the total workload – and the associated costs – would increase substantially. To make the implementation of MDT possible in any control programme, important changes had to be made in almost all control procedures then in use (11, 12). In addition, a complete reorganization of leprosy services was absolutely essential before MDT could be introduced, and this required that a detailed plan of
operations for MDT implementation be prepared and important additional human and financial resources secured. It was therefore expected that leprosy control coverage based on MDT would have to be effected in a phased manner in every endemic country.

The principal role of LEP in the tremendous task that lay ahead was to promote the new strategy and to assist endemic countries with implementation by providing increased technical cooperation, mobilization and coordination of all necessary additional inputs, and continuous assessment.

In 1985, four years after the Study Group meeting, 78,752 patients were reported as being treated with MDT, corresponding to a 1% geographical coverage with MDT at global level (15). This figure, while modest, was the first indication of a tangible achievement in MDT implementation – and the first signal that MDT coverage might increase in subsequent years. The most significant of the successive steps that marked progress from the recommendations to the start of the implementation are outlined in the following paragraphs.

**Significant steps in the introduction of MDT**

At the 14th General Assembly of ILEP, held in Amsterdam in June 1982, members fully endorsed the recommendations of the ILEP Medical Commission that WHO’s new policy be applied in the treatment of leprosy, and adopted a resolution to ensure implementation in the field of the new approach (16). Nevertheless, the German Leprosy Relief Association continued to support the use of MDT based on rifampicin and Isoprodian® in a number of projects. In the early 1980s, ILEP provided annual contributions to LEP that ranged from US$ 400,000 to US$ 800,000, and ILEP member associations were supporting projects that reportedly covered a total of about 1.2 million leprosy patients (17). In 1983, the Damien Foundation of Belgium, an ILEP member association, established a drug fund for MDT with an initial endowment of US$ 400,000, and a number of other ILEP associations provided additional grants to the fund.

The Japan Shipbuilding Industry Foundation (JSIF) accepted the new WHO recommendations on MDT immediately and without reservation. As a consequence, US$ 600,000 of the annual JSIF grant for 1982 was available for WHO-supported activities related to the preliminary steps in MDT implementation at all levels (17). In the subsequent years, the JSIF contributions were increased and could be used as necessary for MDT-related activities.

In August 1982, a WHO meeting on action plans for leprosy control (18) was organized in New Delhi and attended by all WHO Regional Advisers for leprosy and representatives from international, bilateral, and voluntary agencies. The meeting made recommendations on most aspects of MDT implementation: priorities for introduction of MDT; optimal strategy for case-detection and case-holding; integrated services and primary health care; reorganization of leprosy control services; outline plan of operations at country level; mechanisms for strengthening cooperation between governments, contributing agencies, and WHO to mobilize financial resources.

In September 1982 and September 1983, respectively, the WHO Regional Committees of the South-East Asia and Western Pacific regions endorsed the implementation of WHO-recommended MDT regimens (16). Meetings to prepare plans of action for MDT implementation in regional leprosy programmes were held in the WHO South Pacific
subregion (19) (June/July 1982), the Eastern Mediterranean (20) (Mogadishu, October/November 1982), and South-East Asia regions (21) (New Delhi, December 1983) and in Manila (October 1984) for both the Western Pacific and South-East Asia (22).

Meeting in November 1983, the WHO Study Group on epidemiology of leprosy in relation to control discussed important technical issues not covered by the 1981 Study Group on chemotherapy and made precise recommendations on practical aspects of monitoring the implementation of MDT (23):

- a set of working definitions that included:
  - definition of adequate treatment, i.e. the maximum period over which the total prescribed treatment could be completed, for both MB and PB cases;
  - definition of surveillance after completion of treatment (then considered as important);
- precise sets of epidemiological and operational indicators in leprosy control, including those for monitoring MDT.

By 1984, some governments, including those of Ethiopia and India, had held national meetings, and in some cases formed national committees, and adopted WHO MDT and initiated its introduction (16). At the same time, joint efforts between governments, contributing agencies, and WHO were being made to introduce MDT in other projects, countries, and geographical areas (Caribbean countries, Fiji, and India) (16).

In 1983, with a revision in 1984, the member associations of ILEP issued a booklet entitled *The introduction of multidrug therapy for leprosy*, which referred exclusively to the 1981 WHO recommendations for MDT and gave priority to the provision of technical and financial assistance to their projects for the effective introduction and use of MDT (24).

A WHO consultation on implementation of MDT for leprosy control (25), held in Geneva in October 1985, was important for a number of reasons:

- “…virtually all endemic countries either had commenced or were in the process of commencing the implementation of MDT in leprosy control programmes”.
- There was evidence of good acceptability and excellent tolerance of the WHO MDT regimens.
- There was also some evidence that the regimens were capable of preventing and overcoming dapsone resistance.

In preparation for the meeting, LEP had obtained detailed reports on experience of MDT implementation in 27 projects in 22 countries (including three THELEP field trials: MDT for MB leprosy in Karigiri and Polambakkam, MDT for PB leprosy in Malawi, and two projects using the combination of rifampicin and Isoprodian®). These reports were carefully analysed; a working paper summarized the field experience and identified a number of points for discussion from which it was possible to draw lessons and make recommendations for future action (26).

WHO efforts

Since MDT was a methodology newly recommended by WHO and relatively complex to implement, it was obviously part of WHO’s role to advocate its implementation among all concerned and to provide technical assistance. Moreover, the implementation of this new methodology required the mobilization of important additional technical and financial assistance from a number of partners, and WHO had therefore also to play an important coordinating role. These three elements – advocacy, technical assistance, and coordination –
characterized all WHO efforts in promoting MDT during the first few years, as summarized in Table 6.3. The activities with which LEP was most concerned during the years immediately after the Study Group meeting were:

- technical meetings, especially those sponsored by WHO at global and regional levels, at which the rationale of MDT regimens and problems related to their implementation were discussed and possible solutions identified; and
- negotiations with representatives of contributing agencies, essentially JSIF and ILEP and some ILEP member associations.

➢ WHO technical meetings

Technical meetings were the most important means used by WHO for promoting MDT and providing technical assistance to endemic countries, at both global and regional levels, in order to prepare the introduction of MDT. In due course they were also used to monitor the progress of early activities related to MDT. The meetings were organized at the initiative of either a regional office or headquarter (LEP), although both levels cooperated closely in planning and organization. Care was being taken to invite all current or potential partners to meetings in efforts to secure the cooperation – including financial contributions – from all those who were or might be interested. A list of these meetings is given in Table 6.4.

Table 6.4 shows that WHO headquarters (LEP) and the Regional Offices for South-East Asia and Western Pacific were particularly active in stimulating MDT implementation. The Regional Office for the Eastern Mediterranean, in an area where leprosy was less prevalent, organized a meeting in 1982 to discuss activities in preparation of MDT implementation (20). The Pan American Health Organization/WHO Regional Office for the Americas, covering another area where leprosy was less prevalent, organized a sub-regional workshop for five Andean countries and national workshops in three other countries in 1982 (16). Training courses on MDT were organized in the leprosy institutes of Caracas (Venezuela) and Bauru (Brazil), and the recommendations of the 1981 WHO Study Group were presented at several other meetings on general public health problems.

By 1984, the Regional Office for Africa had supported national workshops and training courses on MDT in six countries (16). WHO MDT was also discussed on other occasions, for example at the Conference of OCEAC (Organisation pour la lutte contre les endémies en Afrique centrale) in April 1982. Generally, however, despite the high prevalence of leprosy in many African countries, the Regional office for Africa, did not take an active stance with regard to MDT implementation: a general meeting for that purpose was organized for the Sub-Region 1 of the African region for the first time in December 1986, in Abidjan (27).

➢ Discussions with contributing agencies

Since it was obvious that the global acceptance of MDT regimens, the changes in strategy, and the greater associated costs would require special increased efforts from all contributing agencies (ILEP, JSIF, etc.), LEP was particularly aware during these years of all likely opportunities for discussions and negotiations with these partners. Not only were they invited to WHO meetings (see Table 6.4), but LEP was also keen to attend their meetings whenever possible and to facilitate contacts and discussions between contributing agencies and governments representatives, especially during World Health Assemblies.
Discussions at regional office and country levels

Discussions and negotiations between representatives of governments, contributing agencies, regional advisers for communicable diseases/leprosy, and WHO representatives were also taking place at regional office and country level. Certainly, many decisions from governments on MDT implementation were influenced by the assistance provided to governments by regional offices and WHO representatives, of which there are few records. One of the outcomes of this type of negotiation was the recruitment of WHO consultants to assist governments in the preparation of the national plans for MDT implementation.

THELEP

The Study Group regimens had been recommended without previous evaluation in controlled trials. Trials for concomitant evaluation were therefore essential, and THELEP members of the Study Group assumed that responsibility during the meeting. Trials of the regimens were subsequently undertaken as reported in section 6.2. THELEP also took an active part in the advocacy of the 1981 Study Group regimens, publishing a number of reports on the results of these trial as well as papers on their justification, such as that by Ellard (28) in 1984. Some THELEP leaders participated in a number of technical meetings on the MDT regimens recommended by the Study Group, notably the sixth meeting of the WHO Expert Committee on Leprosy (29) which endorsed the regimens.
<table>
<thead>
<tr>
<th>Date</th>
<th>Steps with significant LEP involvement</th>
<th>Other steps</th>
</tr>
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<tbody>
<tr>
<td>30 November – 5</td>
<td>Meeting on immunology of leprosy, New Delhi</td>
<td></td>
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<tr>
<td>December 1972</td>
<td></td>
<td></td>
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<tr>
<td>August 1973 – 1974</td>
<td>T. Godal drafting a plan for IMMLEP</td>
<td></td>
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<tr>
<td>May 1974</td>
<td>Resolution WHA27.52 on research in tropical diseases</td>
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<tr>
<td>June 1974</td>
<td>A WHO Intra-Secretariat Planning Group established for developing proposals for the</td>
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<tr>
<td></td>
<td>Special Programme for Research and Training in Tropical Diseases (TDR)</td>
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<tr>
<td>August 1974</td>
<td>IMMLEP proposed as pilot activity for the planned TDR</td>
<td></td>
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<tr>
<td>November 1974</td>
<td>4–8 November: First meeting of IMMLEP Project Group</td>
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<tr>
<td></td>
<td>12–15 November: Planning Group meeting on TDR</td>
<td></td>
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<tr>
<td>1975–1976</td>
<td>Detailed proposals for TDR developed</td>
<td></td>
</tr>
<tr>
<td>28–30 April 1976</td>
<td>Planning meeting for the THELEP Task Force</td>
<td></td>
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<tr>
<td>December 1976</td>
<td>TDR set in motion</td>
<td></td>
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Table 6.2
WHO Study Group, 1981: Chemotherapy of leprosy for control programmes. Summary of roles of THELEP and LEP, including preparation of the meeting and implementation of MDT

1. Role of THELEP

- 1976–1980:
  - To organize dapsone resistance surveys unequivocally demonstrating the need for MDT regimens
  - To establish the rationale for the composition of MDT regimens for MB (and PB) patients based on monthly doses of rifampicin

- 1979 onwards:
  - To organize trials of MDT regimens for MB patients

- 1980–1981:
  - To take an essential part in the preparation and discussions of the 1981 WHO Study Group on chemotherapy of leprosy for control programmes

- 1981 onwards:
  - To organize the field trials required to validate the 1981 study group regimens for MB and PB patients
  - To participate in advocacy for these regimens
  - To participate in meetings where these regimens were endorsed (notably the sixth meeting of the WHO Expert Committee on Leprosy)

2. Role of LEP

- By organizing the 1981 WHO Study Group meeting, in close collaboration with THELEP:
  - To prompt the finalization of MDT regimens for MB and PB patients applicable in the field
  - To ensure that these regimens would be recommended for immediate use

- Actively to promote the introduction and implementation of MDT regimens, in cooperation with all partners (see Table 6.3).
Table 6.3
Introduction and implementation of 1981 WHO Study Group MDT regimens for leprosy: summary of the roles of LEP and WHO network

Advocacy and/or technical cooperation predominant
- WHO technical meetings on MDT and leprosy control at:
  - global,
  - regional/sub-regional, and
  - inter-country levels.
- WHO support to courses, workshops, etc., at various levels
- Participation in technical meetings organized by other agencies (International Leprosy Congress, Sasakawa Memorial Health Foundation, International Federation of Anti-Leprosy Associations, International Union Against Tuberculosis, etc.)
- Visits by LEP officers and regional advisers for leprosy to: countries, institutions, contributing agencies, etc.
- Special importance of WHO country representatives: advocacy, technical cooperation and coordination
- WHO consultants

Coordination role predominant
- Discussions at the World Health Assembly
- Discussions with contributing agencies (Sasakawa Memorial Health Foundation, ILEP and member associations, UNICEF, etc.).
<table>
<thead>
<tr>
<th>Date and place</th>
<th>Title of meeting</th>
<th>Organizer</th>
<th>Attendance (in addition to organizer)</th>
<th>Main subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5 March 1982 Manila</td>
<td>Scientific Group on Tuberculosis and Leprosy Research</td>
<td>WPRO</td>
<td>8 countries in Western Pacific region, WHO/HQ (LEP/TB)</td>
<td>Research First national meeting at which the Study Group MDT was discussed</td>
</tr>
<tr>
<td>28 June – 2 July 1982 Suva, Fiji</td>
<td>Seminar on Drug Policy for Leprosy Programmes in the South Pacific</td>
<td>WPRO</td>
<td>16 countries in the subregion NZLTB LEP</td>
<td>Conditions for making MDT implementation feasible</td>
</tr>
<tr>
<td>23–25 August 1982 New Delhi</td>
<td>Meeting on Action Plans for Leprosy Control</td>
<td>LEP</td>
<td>Regional advisers for leprosy SMHF ILEP/5 member organizations ILA</td>
<td>Detailed analysis of leprosy situation in all WHO regions In-depth review of conditions for MDT implementation Review of activities to be undertaken in conjunction with MDT implementation</td>
</tr>
<tr>
<td>30 October – 5 November 1982 Mogadishu</td>
<td>Second Meeting on Strategy for Leprosy Control</td>
<td>EMRO/SMHF</td>
<td>8 countries in Eastern Mediterranean region</td>
<td></td>
</tr>
<tr>
<td>20–23 December 1983 New Delhi</td>
<td>Inter-Country Meeting on Multidrug Therapy in Leprosy Control in the South-East Asia Region</td>
<td>SEARO</td>
<td>8 countries in South-East Asia region LEP 3 VAs from Europe UNICEF</td>
<td>Country profiles for leprosy action plans for implementation of MDT Indicators for leprosy control based on MDT</td>
</tr>
<tr>
<td>24 February 1984 New Delhi</td>
<td>Coordinating Meeting on Implementation of Multidrug Therapy in Leprosy Control</td>
<td>SEARO</td>
<td>All regional advisers for leprosy ILEP/10 member organizations</td>
<td>Plans for MDT implementation exist in most countries. MDT implemented in a number of pilot projects. Statements by VAs Monitoring of MDT implementation could be based on the set of essential indicators prepared by the 1983 Study Group on Epidemiology of Leprosy in Relation to Control, which is close to ILEP revised Form B</td>
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<td>25–29 October 1984 Manila</td>
<td>Interregional Meeting on Multidrug Therapy Regimens for Leprosy Control</td>
<td>SMHF/LEP/ WPRO/ SEARO</td>
<td>22 countries in South-East Asia and Western Pacific regions 8 VAs</td>
<td>Country reports Statements by VAs Planning for MDT</td>
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<tr>
<td>Date and place</td>
<td>Title of meeting</td>
<td>Organizer</td>
<td>Attendance (in addition to organizer)</td>
<td>Main subjects</td>
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<tr>
<td>16–19 October 1985</td>
<td>Consultation on Implementation of Multidrug Therapy for Leprosy Control</td>
<td>LEP</td>
<td>Experts and leprosy programme managers (in personal capacity)</td>
<td>All endemic countries had started or were in the process of starting to implement MDT Analysis of problems based on detailed reports of 27 projects on MDT implementation Integration of leprosy control based on MDT into the primary health care system</td>
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<tr>
<td>16–18 June 1986</td>
<td>Consultation on Implementation of Leprosy Control through Primary Health Care</td>
<td>LEP (SDS, HSH)</td>
<td>Programme managers from countries (in personal capacity)</td>
<td>Integration of leprosy control based on MDT into the primary health care system</td>
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<td>Geneva</td>
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<tr>
<td>4–5 November 1986</td>
<td>Second Coordinating Meeting on Implementation of Multidrug Therapy in Leprosy Control</td>
<td>LEP</td>
<td>All regional advisers for leprosy except from the European region VAs</td>
<td>Cooperation with international, bilateral, and voluntary organizations in the implementation of MDT</td>
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<td>Geneva</td>
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<tr>
<td>2–5 December 1986</td>
<td>Meeting on Leprosy Control in the Countries of Subregion 1</td>
<td>AFRO</td>
<td>11 countries in the subregion 3 leprosy institutes OCCGE OCEAC FFF</td>
<td>Review of national leprosy programmes Problems related to MDT implementation</td>
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<td>Abidjan</td>
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References


6.2 THELEP

L. Levy

The author wishes to acknowledge the invaluable assistance provided by Dr Gordon A. Ellard and Professor Ji Baohong in the preparation of this section.

The Programme for Research on the Chemotherapy of Leprosy, THELEP, began in April 1976 with the meeting of the THELEP Planning Committee (1), which commissioned the preparation of a standard protocol for controlled clinical trials of combined chemotherapy among previously untreated MB patients (2). The primary focus of the trials was to be the detection of persisting \( M. leprae \) by the inoculation of thymectomized, irradiated mice with approximately \( 10^5 \) organisms per hind footpad. At the first meeting of the THELEP Scientific Working Group (SWG), in April 1977, a draft standard protocol was reviewed, amended, and adopted, experimental combined-drug regimens were designed, and applications were approved from the Institut Marchoux, Bamako, Mali, and the Central Leprosy Teaching and Research Institute, Chingleput, South India, to conduct trials of the regimens, and from the National Institute for Medical Research (NIMR), London, England, to inoculate mice with \( M. leprae \) recovered from biopsy specimens to be obtained at intervals from the patients recruited into the trials in Bamako and Chingleput and shipped to the London laboratory. In addition to the attempt to detect persisting \( M. leprae \), the pretreatment susceptibility to dapsone of the patients’ organisms was to be measured by inoculation of intact mice at St George’s Hospital Medical School, London. The results of these trials are reviewed below under “THELEP controlled clinical trials”.

Surveys of dapsone resistance

Even after Pettit & Rees (3) first demonstrated, in 1964, relapse caused by the emergence of dapsone-resistant \( M. leprae \), the importance of this phenomenon was not immediately appreciated. Investigators who had been working in the area of the chemotherapy of leprosy were fully conversant with the evidence that drug-resistant strains of \( M. tuberculosis \) were certain to emerge among tuberculosis patients treated for even brief periods of monotherapy with any of the available bactericidal agents. However, relapse caused by the emergence of dapsone-resistant \( M. leprae \) at first appeared to be extremely rare, perhaps because of the enormous therapeutic ratio – approximately 500:1 (4). Only much later did it become apparent that secondary resistance to dapsone had become a widespread phenomenon (5), and instances of primary resistance were detected (6).

THELEP supplied the protocol for, and supported surveys of, primary dapsone resistance in Addis Ababa (6), which yielded a prevalence of 67 per 100 patients at risk, and Cebu (7), which yielded a prevalence of only 3–6 per 100. In addition, approximately 37% of the patients recruited into the THELEP trials of combined chemotherapy in Bamako and Chingleput were found to harbour \( M. leprae \) with primary dapsone resistance (8, 9). The alarmingly high prevalence of primary dapsone resistance in Addis Ababa, Bamako, and Chingleput suggested that patients who relapsed during dapsone monotherapy infected their
contacts with dapsone-resistant *M. leprae*. This situation appeared to represent a serious threat to efforts to control leprosy, and led directly to the convening of the WHO Study Group.

**Information regarding antileprosy drugs**

From its inception, THELEP set as one of its priorities studies of drugs known or expected to exert antimicrobial activity against *M. leprae*. Among the studies subsequently supported by THELEP were the screening of compounds for antimicrobial activity and clinical trials of promising new drugs and drug combinations.

**Drug screening**

With support from THELEP, a large number of compounds were screened for activity against *M. leprae*. The studies employed both *M. leprae* and batteries of cultivable mycobacterial species, and tested representatives of many classes of compounds, including analogues of cycloserine, dapsone and rifampicin, as well as series of thiosemicarbazones, thioamides, cephalosporins, macrolides, and inhibitors of dihydrofolate reductase (10).

**Clinical trials**

**THELEP controlled clinical trials**

In Bamako and Chingleput, 215 patients were recruited into the two THELEP controlled clinical trials, and 769 biopsy specimens were shipped to London for inoculation of mice. The results of these trials, reported in a series of publications (8, 9, 11–16), may be summarized as follows:

- More than one-third of the patients were found to harbour dapsone-resistant *M. leprae* in the biopsy specimens obtained before treatment with the experimental regimens began.
- Persisting *M. leprae* were detected in approximately 9% of all biopsy specimens.

Detection of the persisters appeared to be a random event, in that these organisms were detected with approximately the same frequency in specimens obtained after 3, 12 and 24 months, regardless of the treatment regimen. In addition, the frequency with which persisting organisms were detected in more than one specimen from the same patient was no greater than that predicted by chance.

- Long-term “field” trials at Karigiri and Polambakkam
  
  At the first meeting of the THELEP SWG in April 1977, it was decided that THELEP could not ethically discontinue treatment once patients had completed two years of therapy with the experimental combined-drug regimens: it was feared that a significant proportion would relapse once treatment was withdrawn. Two years later, however, at its second meeting, the THELEP SWG learned of work in Sungei Buloh (17) and Malta (18), which suggested that the risk of relapse after withdrawal was very small among patients who had been correctly treated with the new regimens; in Malta, no clinical evidence of relapse had been observed among 116 patients with MB leprosy, although 10 patients were found to have positive skin-smears at the time of review. These results encouraged the SWG to conduct “field trials” in Polambakkam and Karigiri, both in South India, in
which large numbers (approximately 400 per regimen) of bacteriologically negative MB patients, previously treated by dapsone monotherapy, were given a combined-drug regimen for two years after achievement of skin-negativity, after which treatment was withdrawn and the patients were observed for evidence of relapse.

The treatment consisted of a total of 1200 mg/month rifampicin given in two consecutive daily doses of 600 mg; a total of 1200 mg/month clofazimine, also given in two consecutive daily doses of 600 mg; 225 mg acedapsone (diacetyl dapsone) intramuscularly every two months; and dapsone 100 mg daily. It later served as a model for the MDT regimen recommended for MB leprosy by the WHO Study Group.

Trials of WHO MDT regimens

- MB leprosy
  Immediately following the 1981 meeting of the WHO Study Group, THELEP added a second regimen – that recommended by the Study Group for treatment of MB leprosy, the WHO MDT regimen – to the “THELEP regimen” used in the Karigiri and Polambakkam trials described above. Newly recruited patients in Polambakkam and Gudyattham Taluk, south India, were randomly assigned to treatment with either the THELEP or the WHO MDT regimen. Almost no relapses occurred among the more than 2200 patients treated by either regimen (19–22).

- PB leprosy
  THELEP sponsored two field trials of chemotherapy among patients with PB leprosy – one in Indonesia and the other in Malawi. Only the results of the Malawi trial were published (23, 24).

Participation in the 1981 Study Group and in subsequent technical meetings related to chemotherapy of leprosy

The Study Group included approximately equal numbers of laboratory and field workers; all of the former group were members of the THELEP SWG. The field workers, in particular, welcomed the Study Group’s conclusion that rifampicin should be administered intermittently, since they were concerned about the cost of this expensive drug and the operational difficulty of supervising each dose. Intermittent administration of rifampicin would permit “stretching” the potentially limited supply of the drug and facilitate the supervision of each dose.

References


6.3 Evolution in WHO, including TDR/THELEP, from 1991 to 2000

Intensive elimination strategy

S.K. Noordeen

The start of the 1990s saw some evidence of stagnation in MDT implementation. The smaller and better-organized leprosy programmes and those that were better-funded were able to introduce MDT early and achieve results. In some of the larger countries, however, MDT coverage was only partial and progress was slow for various reasons including insufficient political commitment and inadequate funding for MDT drugs. Some did not fully appreciate the unique opportunity provided by MDT to bring about the end of leprosy as a public health problem.

It was under these circumstances that the Executive Board of WHO took up the issue of leprosy control in January 1991. A draft resolution for the subsequent World Health Assembly, introduced by the Board member from Nigeria, clearly recognized the potential of MDT to conquer leprosy and declared WHO’s commitment to eliminating the disease as a public health problem by 2000, defining elimination as reducing the prevalence to below one case per 10,000 population. The draft resolution also recognized the substantial progress made in leprosy control, the increasing support from NGOs and other donors, and the growing priority for leprosy control in many countries. It urged Member States to increase political commitment and coordinate all available resources to extend MDT coverage and case-finding, to strengthen training and information systems, and to integrate leprosy control into general health services. The resolution requested the Director-General of WHO to strengthen technical support to Member States, to mobilize additional resources and promote coordination with NGOs, and to strengthen national capabilities and leprosy research.

The Board overwhelmingly supported the draft resolution. In May 1991, when the draft resolution was discussed at the World Health Assembly, it was sponsored by several countries, including China, India, the Netherlands, Nigeria, and USA, and was adopted unanimously.

Following the adoption of the resolution, a number of countries were able to strengthen their commitment and increase the priority accorded to leprosy elimination. International NGOs also increased their support for national leprosy programmes, although ILEP had some reservations – later to prove unfounded – about the impact on fundraising of the message on leprosy elimination. The leprosy research community was also concerned about the diminishing financial support for research, attributing it to funding agencies regarding leprosy as a disappearing problem as a result of the promotion of elimination.

In spite of these developments, many national programmes and major donors such as The Nippon Foundation saw an excellent opportunity to push ahead towards the goal set by the World Health Assembly and were keen to mobilize the necessary additional resources, including those required for MDT drugs. To accelerate this positive trend, WHO took another major step and brought together major leprosy-endemic countries, NGOs, and donor agencies through the First International Conference on Elimination of Leprosy held in Hanoi.
in July 1994. This Conference not only helped in further consolidating political commitment but also provided the opportunity for The Nippon Foundation to announce that it would donate US$ 50 million to WHO for five years for the purchase of MDT drugs. This enabled WHO to meet the drug requirements of all the countries in need: since 1995, no registered patient has had to forego treatment for want of drugs. This “drug security” played a key role in increasing MDT coverage to almost 100% of registered cases within a couple of years following the Hanoi Conference.

The political commitment of the most endemic countries was further strengthened through the Second International Conference on Elimination of Leprosy, held in New Delhi in October 1996. By that time, the leprosy elimination strategy has been universally accepted by everyone including the international NGOs. When the Third International Conference took place in Abidjan in September 1999, the overall situation was quite promising in most of the countries, although it was clear that some – including larger countries such as Brazil and India – needed more time to reach their goal at the national level.

At about this time too, the continued supply of MDT drugs – beyond the year 2000 – was also assured through the generous undertaking by Novartis to meet drug needs for the next five years. This was most reassuring to the countries, which would otherwise have faced serious problems in this regard.

Other developments that facilitated progress towards leprosy elimination included the simplification of technical requirements, which was made possible by the recommendations of the 1994 WHO Study Group on chemotherapy of leprosy and the seventh meeting of the WHO Expert Committee on Leprosy in 1998.

WHO played a key role in coordinating the various agencies interested in leprosy, particularly in relation to national leprosy programmes. Conferences on elimination of leprosy in 1994, 1996, and 1999 greatly facilitated the coordination efforts and made it possible to formalize them through a mechanism of the Global Alliance for Elimination of Leprosy. The Global Alliance was set up in 1999 and has so far met in 2001 in New Delhi and again in Brasilia in 2002.

Changes in research focus

L. Levy

The author wishes to acknowledge the invaluable assistance provided by Dr Gordon A. Ellard and Professor Ji Baohong in the preparation of this section.

New compounds highly bactericidal for Mycobacterium leprae

Identification of compounds

In work supported by THELEP, a number of new compounds with bactericidal activity against M. leprae were identified by Grosset and Ji. These compounds include the fluoroquinolones pefloxacin (1), ofloxacin (2, 3), sparfloxacin (4, 5), moxifloxacin (6), the macrolide clarithromycin (7, 8), the tetracycline minocycline (8, 9), and the rifamycin
rifapentine (6, 10–13). Studies revealed that clarithromycin, minocycline, ofloxacin, and sparfloxacin exert a similar degree of bactericidal activity against \textit{M. leprae}, and, although they are less potent than rifampicin, they are significantly more active than either dapsone or clofazimine alone. Moxifloxacin is the first and, thus far, the only non-rifamycin to display a degree of activity virtually identical to that of rifampicin in mice; it is far more bactericidal than ofloxacin, clarithromycin, and minocycline. Rifapentine is more powerfully bactericidal against \textit{M. leprae} than either rifampicin or the rifampicin–ofloxacin–minocycline (ROM) combination.

These results clearly demonstrated that screening existing compounds is the most cost-effective approach to drug development in leprosy. They also indicated that it is most productive to screen compounds that display powerful activity against a wide spectrum of Gram-positive micro-organisms in general or cultivable mycobacteria in particular, or that exhibit more favourable pharmacokinetic properties than those of the member of the class currently used to treat leprosy (6).

\textit{Short-term trials in MB leprosy}

Short-term trials require the recruitment of only 6–10 untreated MB patients per regimen. Treatment is administered either as a single dose or for no longer than a few months; skin lesion biopsies are taken at intervals during treatment, and the \textit{M. leprae} recovered from the biopsy specimens are inoculated into mice. After treatment with the experimental drug or regimen has been completed, patients are treated with MDT as if they had not previously been treated.

Immediately after the active new drugs had been identified by screening in \textit{M. leprae}-infected mice, short-term clinical trials of pefloxacin (14), ofloxacin (14–16), clarithromycin (17, 18), minocycline (17, 19), and sparfloxacin (20) were launched; in most trials, the therapeutic effects of the treatment were monitored by mouse footpad inoculation. Treatment with any of these compounds alone had considerable bactericidal activity against \textit{M. leprae}. For example, 99.99% of viable \textit{M. leprae} were killed by 22 daily doses of 800 mg pefloxacin or 400 mg ofloxacin (29), and >99% killing was observed after 28 days of daily administration of 100 mg minocycline, 500 mg clarithromycin (17), or 200 mg sparfloxacin (20). The bactericidal activity of single doses of the combinations clarithromycin–minocycline (18) or ofloxacin–minocycline (15) against \textit{M. leprae} was equivalent to that of four weeks of daily treatment with the dapsone–clofazimine combination; however, the gastrointestinal side-effects associated with large doses of clarithromycin were not well tolerated by patients.

Encouraged by these results, the ROM combination was tested in a clinical trial; a single dose of this combination displayed considerable bactericidal activity against \textit{M. leprae} (15). More recently, following the observations that moxifloxacin exerts a very powerful bactericidal effect on \textit{M. leprae} (virtually identical to that of rifampicin), that rifapentine is far more bactericidal than rifampicin, and that a single dose of the combination rifapentine–moxifloxacin–minocycline (PMM) killed 99.9% of viable \textit{M. leprae}, it appeared likely that PMM would be more efficient than ROM as a fully supervised, monthly-administered multidrug regimen for leprosy (6). A clinical trial is being conducted to compare PMM with
ROM and the moxifloxacin–minocycline combination with ofloxacin–minocycline, in terms of both therapeutic effects and side-effects. The results of this trial will become available shortly.

*The ofloxacin multicentre trial (21)*

In 1991 and 1992, THELEP (now known as THEMYC) launched a large-scale multi-centre field trial, the main objectives of which are to evaluate the efficacy, acceptability, and feasibility of ofloxacin-containing combined regimens in a randomized, double-blind, controlled clinical trial in both MB and PB leprosy patients. One of trial regimens is a combination of rifampicin *plus* ofloxacin daily for 4 weeks for both MB and PB leprosy. The other two regimens, both for MB leprosy, are the WHO-recommended MDT for 1 year, with or without daily ofloxacin supplementation during the first 4 weeks. The control regimen is the standard 24-month WHO-recommended MDT regimen.

The current trial has six arms: four for MB, and two for PB leprosy. For MB leprosy, the four arms are:
- WHO MDT for 2 years
- WHO MDT for 1 year
- WHO MDT for 1 year supplemented by daily ofloxacin for the first 4 weeks;
- ofloxacin plus rifampicin daily for 4 weeks.

For PB leprosy, the two arms are:
- WHO MDT for 6 months;
- ofloxacin plus rifampicin daily for 4 weeks.

Fifteen centres from eight endemic countries are participating in the trial. The intake of nearly 4000 patients was completed in June 1994, and treatment was completed in December 1996. Follow-up will continue until December 2003, and final results are expected to be available by mid-2004.

*Participation in technical meetings after 1981*

After 1981, technical meetings on new antileprosy drugs and their use in combinations included the meeting of a second WHO Study Group, convened in Geneva in November 1993 (TRS 847) in which Dr Jacobson and the author participated, and the seventh meeting of the WHO Expert Committee on Leprosy, convened in Geneva in May 1997, in which Drs Grosset and Ji participated. Finally, the WHO Technical Advisory Group, which included several former members of THELEP/THEMYC, has met on three occasions – in Geneva in May 2000, in New Delhi in February 2001, and in Brasília in February 2002.
References


