

Chapter 3

Implementation of MDT

3.1 Successive steps

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This section attempts to analyse the various aspects of the evolution of MDT implementation from 1982 to date.

Implementation of MDT started gradually, on a pilot basis, over the period 1982–1985; coverage during this time was less than 1%. Subsequently, MDT was implemented in many endemic countries, and the geographical coverage began to increase significantly, reaching almost 50% by the end of 1992 (see Table 3.1).

Table 3.1
MDT coverage from 1985 to 2000

End of year	Registered cases	New cases	Patients treated with MDT	Cumulative total cured with MDT	Geographical MDT coverage
1985	5 368 202	550 224	78 752	9 425	1%
1986	5 341 000	573 790	468 222	93 216	9%
1987	5 078 000	594 145	1 318 964	515 144	26%
1988	4 908 000	553 597	1 604,927	627 919	33%
1989	3 866 000	550 743	1 751 903	853 706	45%
1990	3 737 000	571 792	2 080 998	1 204 821	56%
1991	3 087 788	584 412	1 295 640	2 870 944	42%
1992	2 291 581	653 354	1 117 508	4 238 118	49%
1993	1 671 497	590 933	911 802	5 658 989	55%
1994	1 291 848	560 646	984 005	6 687 189	76%
1995	926 259	529 376	842 438	7 988 404	91%
1996	888 340	566 604	862 998	8 416 321	97%
1997	804 396	693 462	803 021	9 095 409	100%
1998	820 205	804 449	820 205	9 974 000	100%
1999	753 263	738 284	753 263	10 759 213	100%
2000	611 000	655 000	611 000	>11 million	100%
2001	597 232	719 330	597 232	12 million	100%
2002	534 311	620 672	534 311	13 million	100%

However, the definition of MDT coverage was not standardized among countries, and the statistics from 1989 to 1994 should be analysed with caution. During this period India, for example, defined MDT coverage as the proportion of districts in which MDT was implemented; thus, even if only one health facility in a district began implementing MDT, the whole district was considered to be under MDT. Moreover, although the figures reported at that time implied that all registered patients in a district where MDT had been implemented were treated with MDT, this was not the case – most patients continued to get dapsone monotherapy. Information collected later showed that it was only after 1998 that all the patients in India were treated with MDT.

Main events, 1982 onwards

Four successive periods, or phases, can be identified in the implementation of MDT:

- 1982–1985 – Introduction of MDT on a global basis
- 1986–1990 – Expansion of MDT (into the “less difficult” areas)
- 1991–1999 – Elimination strategy
- 2000 onwards – a fourth period, planned to last 6 years, designated for the “Intensive elimination strategy” or the “Final push”.

1982–1985: Introduction of MDT

During the 4 years 1982–1985, the use of MDT as recommended by the 1981 Study Group was very actively promoted by WHO and more precisely by headquarters leprosy unit (LEP) and the two Regional Offices for South-East Asia and the Western Pacific (see section 6.1).

The Study Group recommendations on MDT were promptly endorsed by JSIF and ILEP (except, in the latter case, in relation to Isoprodian[®]). From the very first, the active cooperation and financial contributions of these agencies were of critical importance for the implementation of MDT. Not unnaturally, the early “pilot” projects were undertaken in areas where conditions were relatively favourable.

Two meetings proved particularly important to the preparation for, and early steps in, MDT implementation. At a meeting on action plans for leprosy control (1), organized by LEP in New Delhi in August 1982, representatives from WHO headquarters and regional offices and from JSIF and ILEP were able to discuss in detail all the implications of MDT implementation. In October 1985, at a WHO consultation on implementation of MDT therapy for leprosy control (2), the same partners reviewed several MDT implementation projects and began to draw lessons from the experiences of these projects. At that time – 4 years after the Study Group meeting, and 3 years after the publication of its recommendations – global MDT coverage was about 1%.

1986–1990: Expansion of MDT into the “less difficult” areas

The profound changes that were needed in the structure and function of all leprosy control programmes before MDT implementation led to the recommendation that MDT be expanded in a phased manner, covering first the areas with more favourable conditions. Indeed, some countries started MDT only for selected MB patients while a number of others significantly modified the recommended regimen. In general, the areas covered during this period were the less difficult ones. Globally, geographical coverage with MDT increased steadily from 1% in 1985 to around 40% in 1990 – progress that may be considered quite satisfactory under the circumstances.

Understandably, there were no important change in policy during this period. At its sixth meeting, in November 1987, the WHO Expert Committee on Leprosy (3) endorsed the recommendations of the 1981 Study Group regarding the content and duration of MDT regimens and post-treatment surveillance. However, the Committee made a change to the definition of MB and PB cases provided by the Study Group: for the purpose of MDT, all smear-positive cases were henceforth to be included in the MB group. Consequently, good bacteriological services continued to be considered essential for correct MDT implementation.

In 1988, WHO published the second edition of *A guide to leprosy control* (4), incorporating all considerations relevant to MDT and its implementation as well as other aspects of leprosy control.

Strenuous efforts to strengthen cooperation between LEP and WHO's regional offices, as well as among WHO, governments, and voluntary agencies, were made. To this end, two further coordinating meetings on implementation of MDT were held, in November 1986 (5) and September 1988 (6) respectively. At the September meeting, it was pointed out that Africa was far behind other parts of the world in implementing MDT and a meeting was planned for 1989 to decide on the mechanisms by which African countries could catch up (7).

A number of international technical meetings were convened by WHO during this period to discuss methods of accelerating MDT implementation. Subjects of special importance were training in leprosy (8), MDT and primary health care (9, 10), and assessment of the leprosy situation (11, 12).

By the end of 1990, accumulated experience had advanced the thinking on MDT implementation. A consultation on technical and operational aspects of leprosy (13) held in Malé, Maldives, in June 1990 accepted that MDT could be started "even in areas with relatively limited health development and human resources", and concluded that it should be possible to start MDT "even before establishing reliable skin smear services" and that "programmes should consider wider application than hitherto considered of fixed-duration treatment of 24 months of MDT for MB patients".

1991–2000: Elimination of leprosy as a public health problem

In May 1991, the World Health Assembly adopted resolution WHA44.9 (see Appendix 1) on elimination of leprosy as a public health problem, committing the governments of endemic countries to reach the global target prevalence of less than one case per 10 000 population by the year 2000. The rationale of the elimination initiative included the following three points:

- the availability of highly effective treatment (MDT) to cure the disease;
- willingness to change the attitude of passively accepting leprosy as a perennial problem;
- in many endemic countries, the favourable epidemiological trend of a "naturally decreasing epidemic".

The adoption of the WHA resolution by all Member States was a crucial step, which unquestionably allowed the most effective use to be made of the MDT-based elimination strategy. It resulted in a period of intensive expansion of MDT during which geographical coverage increased from 42% in 1991 to 100% in 1997 (and subsequently). Implicit in the elimination strategy was the notion that, with leprosy prevalence reduced to less than one case per 10 000 population, and provided that all cases were detected and all patients cured as a

result of complete MDT coverage, prevalence would continue to decline and the disease would finally disappear (14). This vision, while clearly most appealing from the public health viewpoint, was strongly questioned by some renowned epidemiologists (15).

The elimination phase was essentially characterized by ever-greater efforts to tackle the wide range of problems related to the expansion of MDT coverage to areas or population groups that were increasingly remote or difficult to access. During this phase the Nippon Foundation's pledge of US\$ 50 million, made at the first International Conference on Elimination of Leprosy held in Hanoi in July 1994 (16), for the procurement of MDT drugs over the succeeding five years was of critical importance.

Evolution in technical policy and introduction of new strategies

- At its meeting in November 1993, the WHO Study Group on Chemotherapy of Leprosy, (17) recommended two important simplifications related to MDT implementation:
 - The regimen for MB patients should be of a standard duration of 2 years.
 - Post-MDT annual surveillance of patients should be discontinued.

The Group also suggested some flexibility concerning the use of bacteriological services and relaxed the requirement for supervision by health workers of monthly doses of rifampicin and clofazimine.

In 1992 the gradual introduction of MDT “calendar” blister packs had begun, and WHO began global supply of these packs for fixed-duration MDT for MB and PB patients in 1995.

- *A guide to eliminating leprosy as a public health problem* (18) was published in 1995.
- At its meeting in May/June 1997, the WHO Expert Committee on Leprosy introduced some important changes (19):
 - For purposes of MDT, patients should be classified in three categories:
 - PB leprosy (single skin lesion)
 - PB leprosy (2–5 skin lesions)
 - MB leprosy (more than 5 skin lesions).
 - For MDT regimens, the Committee made the following recommendations:
 - PB leprosy, single skin lesion: a single 600-mg dose of rifampicin plus 400 mg ofloxacin and 100 mg minocycline (ROM) is an acceptable alternative regimen.
 - PB leprosy: no change.
 - MB leprosy: the duration of the current MDT regimen could be reduced to 12 months without significantly lowering its efficacy.

More than one month’s supply of MDT blister calendar packs could be given to the patient whenever necessary. To increase MDT coverage, two new strategies were recommended:

- leprosy elimination campaigns (LECs) in pockets of high leprosy prevalence;
- special action projects for the elimination of leprosy (SAPEL) to reach patients living in remote areas or under difficult conditions.

- Other important documents that provided updated guidelines for implementing the elimination strategy were published in 1994 (20) and 1995 (18).
- At the fourth meeting of the Leprosy Elimination Advisory Group (LEAG), held in Geneva in June 1998, WHO noted that “virtually every patient was receiving MDT” but that “some countries may need to continue and intensify activities beyond the year 2000 to reach their elimination targets” (21).

In April 1999 a special meeting of the LEAG held with potential partners (22) acknowledged that about 12 countries would not reach the national elimination target by the end of the year 2000. The elimination strategy should therefore focus on these 12 countries, intensifying efforts of LECs. A consultative meeting on LECs held in July 1999 reviewed the results of campaigns carried out until that date and provided guidelines for improving their effectiveness (23).

- The Third International Conference on the Elimination of Leprosy (24), held in Abidjan in November 1999, reviewed the status quo (25):
 - The registered global prevalence of leprosy was around 1.4 per 10 000 inhabitants.
 - Almost all leprosy patients were treated with MDT.

Clearly, the elimination process had made tremendous progress and the elimination strategy remained valid. However:

- The number of new cases detected annually remained constant or was increasing.
- Around 735 000 registered cases and 750 000 new cases – which represented 90% of the prevalence and detection worldwide – were found in the 12 most highly endemic countries. Just one year before the target date for elimination, the aggregate prevalence rate in these top endemic countries was still 4.5 per 10 000 inhabitants, more than 4 times the elimination level.

In response to this situation, WHO and its partners launched the Global Alliance for the Elimination of Leprosy (GAEL). The general objective of GAEL was to reach the elimination target prevalence at country level by the end of 2005 by focusing its activities on the 12 top endemic countries; a strategic plan to that end was adopted (26). Financial contributions to GAEL were pledged, notably by The Nippon Foundation/Sasakawa Memorial Health Foundation, the Novartis Foundation for Sustainable Development, and ILEP. Shortly thereafter, however, ILEP withdrew its pledge. The GAEL action plan became known as “The Final Push” (towards elimination).

Advocacy at the highest level and coordination

The most significant efforts made to enhance the commitment and active participation of all partners – principally the major endemic countries themselves – were the three International Conferences on the Elimination of Leprosy. The first of these (16), held in Hanoi, Viet Nam, in July 1994, was organized by WHO at the initiative of its then Director-General, Dr Hiroshi Nakajima, and co-sponsored by the Sasakawa Memorial Health Foundation (SMHF). It was attended by more than 100 participants from a large number of countries (including the 28 with the highest leprosy prevalence at the time). Dr Nakajima announced the creation of a WHO Special Programme for the Elimination of Leprosy, estimating the cost of implementing the elimination plan over the coming 6 years as around US\$ 420 million. Mr Yohei Sasakawa, President of The Nippon Foundation, pledged US\$ 50 million over the next 5 years, which represented one-third of the estimated cost of drugs for MDT.

The second International Conference (27), held in New Delhi, India, in October 1996, was again organized at the instigation of the Director General of WHO and co-sponsored by the SMHF and the Government of India. The 150 participants, from 25 countries, included the health ministers of 14 endemic countries. Emphasis was again placed on the need to accelerate progress in increasing MDT coverage, and the importance of LECs and SAPEL programmes was agreed. It was recommended that the Leprosy Elimination Monitoring initiative (LEM) be implemented as soon as possible. LEM was designed by WHO as standard procedures for the collection and analysis of data required for a set of key indicators on leprosy and its elimination through independent monitors.

The third of the International Conferences (24), again organized by WHO and co-sponsored by SMHF, the Association Française Raoul Follereau, and the Government of Côte d'Ivoire, was held in Abidjan in November 1999. It was at this Conference that the need to extend the elimination plan for a further 6 years was acknowledged and GAEL was established. In 2000, ILEP established official relationships with WHO.

Programme intensification and monitoring

➤ *Action Programme for the Elimination of Leprosy*

In December 1994, the WHO Leprosy unit was replaced by the Action Programme for the Elimination of Leprosy (but continued with the same acronym, LEP). The programme was made up of the following components:

- Office of the Director for overall management
- Country support and special action projects (CSP)
- Monitoring and evaluation of elimination (MEE)
- Capacity building and health systems research (CBH).

➤ *Advisory groups*

Achieving the global elimination of leprosy as a public health problem necessitated the redefining of priorities and strategic plans. In this task, LEP was assisted from 1991 to 1994 by the WHO Working Group on Leprosy Control and from 1995 to 1999 by the Leprosy Elimination Advisory Group (LEAG). These two advisory groups included WHO regional advisers for leprosy, representatives from national and international NGOs (International Leprosy Union – ILU, International Federation of Anti-Leprosy Associations – ILEP, International Leprosy Association – ILA, The Nippon Foundation/Sasakawa Memorial Health Foundation – TNF/SMHF, etc.), other contributing agencies (e.g. World Bank), and individual experts. The LEAG had a larger number of members from the various organizations than the Working Group.

The Working Group and the LEAG held annual meetings (21, 28–34) which were important opportunities for exchanges of views and information between NGOs, other contributing agencies, and WHO representatives from headquarters and regional offices. Regular items on the agenda of these meetings were a review of the current status of the elimination programme at global and regional level (and the most highly endemic countries since 1995), as well as statements from representatives of NGOs and other contributing agencies.

There was full agreement between NGOs – especially ILEP – and WHO on the main final objective of leprosy control activities: in 1990, ILEP had adopted the objective of “MDT for all leprosy patients by the year 2000” which was essentially the same as

WHO's elimination target (28). However, voluntary agencies were unhappy with the definition of a leprosy case used and recommended by WHO, according to which patients "bacteriologically cured" but having residual disabilities were no longer "cases" of leprosy. They were also concerned that the general public would believe that, with the *elimination* of leprosy, the task had been completed and this would adversely affect fundraising activities.

At its first meeting, the Working Group recommended that WHO should establish a task force to promote health systems research (HSR). This task force held three meetings – in 1992 (35), 1993 (36), and 1994 (37) – and organized various workshops and training activities. Following a recommendation made at the fourth meeting of the Working Group (31), two further task forces – Monitoring and Evaluation of Elimination of Leprosy (MEE), and Capacity Building and Health Systems Research (CBH), replacing the original task force on HSR – were established, together with a Steering Committee on Special Action Projects. The activities of these task forces and of the Steering Committee were reviewed at LEAG meetings.

At the first meeting of the LEAG (32), WHO introduced the concept of the LEC, which has proved to be one of the most effective tools for detecting hidden cases. In October 1996, the second meeting of the MEE task force reported to the LEAG that analysis of data from 24 countries for the period 1985–1995 showed a dramatic fall in prevalence, although the number of newly detected cases had remained static (33).

In June 1998, at the fourth meeting of the LEAG, WHO indicated for the first time that "some countries may need to continue and intensify activities beyond the year 2000 to reach their elimination targets". As a consequence, the LEAG recommended that "a long-term comprehensive strategy for leprosy" be developed for presentation in 1999. This appeared as *The final push towards elimination of leprosy: strategic plan 2000–2005*, prepared by the WHO Leprosy Elimination Group (26).

2000 onwards: the Final Push

At the end of 2000, the global prevalence rate was just below one per 10 000 population, enabling WHO and its partners to announce in May 2001 that the overall target set 10 years earlier for the global elimination of leprosy as a public health problem had been reached.

The Strategic Plan

The preface to the Strategic Plan document (26) stated, "Today, we can be confident that elimination – the reduction in prevalence to less than one case per 10 000 population at national level – is within reach in all countries by the end of 2005." The Plan classified the endemic countries in three groups:

- *Group 1*: 12 countries that need special efforts to intensify the elimination strategy (Angola, Brazil, Central African Republic, Democratic Republic of the Congo, Guinea, India, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, and Niger).
- *Group 2*: 12 countries where the elimination strategy should be accelerated.
- *Group 3*: 26 countries where the elimination strategy should be sustained.

In countries of Group 1, “Epidemiological trends over the last 10 to 15 years show high and often increasing detection rates, and geographical coverage with MDT is not complete or has been completed only recently.” In those countries, which represent the core of the problem, the specific activities to be intensively implemented, included:

- enabling all health facilities in endemic districts to diagnose and treat leprosy;
- promotion of case-finding by informing the public about the disease and encouraging individuals with suspicious skin lesions to come forward for treatment;
- changing the community image of leprosy through information, education and advocacy.

In other words, as in previous years, the essential conditions for the success of the elimination strategy in its Final Push, were the integration of MDT services into the general health services, and changing the negative image of leprosy and encouraging people to seek treatment.

The Strategic Plan insisted on the key importance to the integration process of capacity building at local level (i.e. concerning general health workers and community health volunteers). With reference to IEC activities, strategies for promoting community action needed to be developed and sectors other than health involved in the elimination plan. The key role of local community leaders in all aspects of the elimination process was identified, as was the need to improve communication and cooperation with the mass media. The Strategic Plan also mentioned the importance of activities related to drug supply and to surveillance and programme monitoring.

Subsequently, WHO established the Global Alliance for the Elimination of Leprosy (GAEL), responsible for advocacy and coordination at the highest level, and a Technical Advisory Group (TAG), concerned with the intensification and monitoring of the elimination programme.

Global Alliance for the Elimination of Leprosy

GAEL was established during the Third International Conference on Elimination of Leprosy, held in Abidjan, Côte d’Ivoire, on 15 November 1999 (24). The core members of GAEL then comprised governments of major leprosy-endemic countries, WHO (as secretariat), TNF, ILEP, Novartis, the Danish International Development Assistance (DANIDA), and the World Bank (38). The offices of Chair and Vice-chair of GAEL are held by Member State on a rotational basis.

The first meeting of GAEL, held in New Delhi in January 2001, was a kind of forum similar to the three International Conferences on the Elimination of Leprosy, which had taken place during the previous decade. The meeting issued the Delhi Declaration, essentially endorsing the Final Push strategy and recommending that “members of GAEL collaborate in a true spirit of partnership in order to eliminate leprosy as a public health problem from every country by the year 2005”.

Brasília was the venue for the second meeting of GAEL, in January 2002, which was attended by high-level delegates of eight major leprosy-endemic countries, representatives from Novartis Pharma AG/Novartis Foundation for Sustainable Development, TNF/SMHF, TAG members, 20 members of the WHO Secretariat, and 84 State Leprosy Coordinators from Brazil; invited representatives from four other countries and from DANIDA and the World

Bank were unable to attend. Observers from 20 United Nations agencies and NGOs (including 14 ILEP member associations) had been invited, but only the Presidents of SMHF and of the American Leprosy Mission were present; this was a consequence of the withdrawal of ILEP from membership of GAEL (in December 2001).

WHO Technical Advisory Group on Elimination of Leprosy

The TAG is responsible for programme intensification and monitoring – much as the WHO Working Group and the LEAG had been responsible during the previous decade. Recommendations made by the TAG at its first meeting, held in May 2000, may be summarized as follows (40):

- The present *definition of elimination* should be retained. It was noted, however, that additional indicators would be needed.
- There was a need to improve *reporting systems*.
- “Special efforts will be made to raise awareness and enlist political commitment in order that *countries accept ‘ownership’ of their leprosy elimination programmes* at national and sub-national levels.”
- “*National Task Forces* will be established where necessary in endemic countries. These will provide the medium to greatly enhanced collaboration between national leprosy elimination programmes, nongovernmental organizations, donor agencies, the scientific community and all other partners. At the same time, national task forces will play a leading role in ensuring that leprosy elimination programmes become integrated within the general health services.”
- Information, education and communication (IEC): “Primary health care workers need to develop a system of ... advocacy activities ... to assist people to recognize the early signs of leprosy”. “For those without easy access to health services, ‘*accompanied*’ treatment needs to be encouraged.”
- “*Operational research* will be the major research priority for the leprosy elimination programme.”

The second meeting of the TAG (41), held in February 2001, recommended:

- expanding the use of LEM-like exercises;
- developing advice on all aspects of integration using current experiences from integration efforts for other disease-specific programmes.

A TAG subgroup on monitoring and evaluation concluded that the certification of leprosy elimination was not relevant and made a series of detailed recommendations on the use of LEM exercises to provide objective and independent information on progress towards leprosy elimination.

Another subgroup on field studies for strengthening implementation of the elimination strategy identified a number of field studies to be initiated by the Secretariat on: accompanied MDT, integration, relapses following 12 months of MDT and ROM, impact of IEC activities, SAPEL, leprosy in urban areas, use of Prednipacs (each pack containing one standard 12-week course of prednisolone for managing lepra-reactions), MDT regimens of shortened duration, rifampicin resistance, epidemiological models, and leprosy classification systems.

The third meeting of the TAG, in February 2002, made recommendations on various aspects of the elimination strategy; the following two were of special importance (42):

- large-scale implementation of accompanied MDT;
- implementation of a research study using 6-month MB MDT regimen as uniform MDT for all leprosy patients (PB and MB)

One of the conclusions of the TAG subgroup on monitoring and evaluation was that significant numbers of patients are kept on treatment registers even after completion of treatment and these patients should be removed from those registers. (42).

At its fourth meeting, in June 2002 (43), the TAG's main task was to agree on a draft protocol for studying a uniform MDT regimen for all leprosy patients (as indicated above). The protocol was finalized on 20 August 2002. The study is currently being undertaken in several areas/programmes with reasonably well organized leprosy elimination programmes capable of recruiting at least 500 new leprosy patients (250 MB and 250 PB) within 2 years. The patients will be followed for any occurrence of relapses up to seven years after completion of treatment. The final results will be available in 2010.

In view of the alarming increase in the number of new cases detected in some major endemic countries, notably India, this TAG meeting also included a special session on global case-detection trends over the previous 4 years. The trend was paradoxical: information coming from the majority of endemic countries clearly showed that, after repeated LECs, the detection trends showed a significant decline in new cases. It was agreed that these trends in some major endemic countries were mainly the result of a number of operational and administrative shortcomings.

These findings led Dr Neira, in her statement at the 16th International Leprosy Congress (Bahia, Brazil, August 2002), to say that "some countries will not reach the elimination target at the national level by the end of the year 2005".

One might therefore have accepted the view expressed by Professor Lechat when the time target for the elimination was postponed for the first time – that the year 2000 was only a milestone (21). The elimination target, and its time-bound nature, have contributed to increasing the crisis that has developed among the partners of the Global Alliance.

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3.2 Some important factors contributing to the implementation of WHO MDT

M.F. Lechat

Wide acceptance of MDT

Multidrug therapy has been at the core of the leprosy elimination strategy for the past 20 years. The worldwide implementation of MDT has been a considerable success, proving effective in curing the disease and rendering patients non-infectious after a treatment of relatively short duration, with very few subsequent relapses and no emergence of drug-resistant strains of *M. leprae*. Furthermore, the WHO prescription for standard regimens of MDT has resulted in the discharge of millions of patients; in statistical terms, this translates into prevalence rates approaching minimal levels.

In October 1981, when the Leprosy unit of WHO took the initiative of convening a Study Group on the Chemotherapy of Leprosy for Control Programmes (1), documented evidence of the efficacy of MDT in humans was scarce. Clinical field trials were not expected to provide data rapidly, since the end-point of the trials was the observation of relapses that could occur 5–7 years after completion of at least 2 years of treatment. The Study Group was confronted with a dilemma: while field data were lacking and unlikely to become available for several years, leprosy control was faced with the rapidly increasing prevalence of dapsone-resistant *M. leprae* strains which jeopardized more than 30 years of efforts to control the disease by dapsone monotherapy. After much debate, the Group opted for MDT – a momentous decision ultimately justified by the subsequent retreat of leprosy.

How did WHO manage to enforce – or, better, persuade – the leprosy world, from governments to NGOs, laboratory scientists to field workers (and not forgetting the patients themselves) to adopt and accept the standard MDT regimens recommended by the 1981 Study Group? How was success in marketing the new strategy of leprosy control achieved in the face of, inter alia, governments with other priorities, indifferent or ignorant health workers, sceptical scientists, old-fashioned clinicians entrenched in their traditional approaches, and nongovernmental organizations pursuing their own agendas? To the outside observer, the general acceptance of MDT over the past 20 years would seem to be the result of a number of factors – some part of a deliberate plan, other circumstantial. Not all factors were operative at the same time, nor did they necessarily intervene in a logical sequence.

Standardization and simplification of procedures

Notwithstanding the scientific backing for the MDT regimens provided at the fifth meeting of the WHO Expert Committee on Leprosy in 1976 (2) and by the THELEP Scientific Working Group in 1977 and 1979 (3), a major reason for the acceptance of MDT was that it was not presented as solely a pharmacological “recipe”. Its implementation was to be accompanied by modifications in diagnostic and treatment procedures – standardization of the drug regimens, classification of patients into two main clinical categories, and a fixed duration for the treatment. These measures did not develop all at once; they evolved gradually to form what could be called the WHO MDT package.

Standardization of treatment

The 1981 Study Group (1) recommended strictly standard MDT regimens, differing only with the clinical type of patient. Standardization of regimens was doubtless extremely important in accelerating acceptance of MDT: not only did it facilitate the procurement of drugs – it was also patient-friendly and convenient for field workers. In 1987, the availability of calendar blister packs was a crucial improvement in the drug delivery process.

Case definition and diagnosis

For years, the diagnostic criteria and clinical classification of leprosy were the object of heated debate. Eventually, the decision was made to adopt a case definition based on the clinical signs of the disease for detection purposes, and on the number of skin lesions for operational categorization with respect to the choice of MDT regimen. Thinking on the role of bacteriological examination changed gradually. The 1981 Study Group (1) still considered bacteriological examination to be “very important and highly relevant to leprosy control”, yet in November 1987, at the sixth meeting of the WHO Expert Committee, its poor quality was recognized as “the weakest link in most control programmes” (4). At its seventh meeting, 10 years later, the Expert Committee (5) stated that, while skin smears “are useful”, “since it is possible to classify leprosy without skin smear results, there is no need to establish skin smears services. Such services should not be a prerequisite for implementing MDT.” This statement ratified a de facto situation: what had been tolerance became a prescript, and the simplification doubtless facilitated the life of the leprosy field worker and contributed to wide acceptance of MDT.

Duration of the treatment

Dapsone monotherapy, used since the 1940s, required more than 5 years of regular treatment to render most, but not all, lepromatous (multibacillary) patients eligible for discharge. By contrast, MDT was effective within a short time, possibly even weeks. The consequent recommendations were that the treatment of MB patients be continued for at least 2 years and, whenever possible, up to smear negativity (1, 4). Treatment for PB patients was to be given for 6 months.

At its seventh meeting in 1997, the WHO Expert Committee (5) stated cautiously that “it is possible that the duration of the current MDT regimen for MB leprosy could be further shortened to 12 months without increasing the risk of developing rifampicin resistance”. This was by and large interpreted as a recommendation to stop all treatments after 12 months.

In view of the threat of drug resistance, the recommendation for a standard multiple chemotherapy was well received and widely accepted by a large number of researchers, managers of leprosy control programmes, and NGOs. The Medical Commission of ILEP endorsed the WHO recommendations regarding standard MDT regimens (6) – an important consensus, since ILEP coordinates the activities of 22 NGOs that support leprosy control in more than 100 endemic countries. In some circles, however, the recommendations met with a degree of resistance or at least were accepted with reluctance. Some academics and private practitioners tended to favour more accurate diagnosis, more sophisticated MDT regimens, or treatment of longer duration, all of which had the disadvantage of making treatment generally

more costly (though not less effective). As the effectiveness of standard MDT became apparent, and large quantities of free drugs were supplied by or through WHO or NGOs, this resistance gradually evaporated.

The decision to enforce reduced duration of the treatment of MB patients (to 1 year) was criticized by a number of scientists and programme managers, who considered that the modification had been made on the basis of insufficient evidence and of an abusive interpretation of the Committee's statement. This controversial matter was never openly debated, either at subsequent congresses and meetings or on the Internet; no doubt, however, it helped to increase the coverage of MDT.

Epidemiological intelligence

The development of epidemiological intelligence contributed significantly to the success of MDT. Assessing the size of a problem is a prerequisite for health authorities at all levels to decide priorities, take appropriate decisions, monitor activities, and evaluate results.

In 1976 – in advance of the 1981 recommendations on MDT – and working through a university department affiliated to its network of collaborating centres, WHO fostered the collection and retrieval of relevant statistics in leprosy-endemic countries by sponsoring the development of a recording and reporting system for leprosy patients – OMSLEP. This system became operational in 1980. As stated at the time, “... the information compiled should be as simple as possible, so that it can be collected at the periphery by multipurpose health workers with the minimum of specific training. This requires the identification and selection of the minimum information necessary to evaluate the progress of control activities.” (7).

As early as 1982, computerization of the system was being mooted on the assumption that “mini” (later, personal) computers be used increasingly in the health services of endemic countries, making it possible to produce reliable and continuously updated information. A workshop was organized in Kuala Lumpur, in cooperation with SMHF, to familiarize leprosy workers from south-east Asia and western Pacific regions with the system (8). These activities raised awareness among health authorities and professionals of the importance of leprosy as a public health problem. Overall, the wide acceptance of MDT was one of the main factors that prepared the ground for the momentous World Health Assembly resolution WHA44.9 in May 1991, which declared WHO's commitment to global elimination and urged Member States to give it full political support.

Extremely low relapse rates after MDT treatment

The reappearance of acknowledged signs of active disease in a patient declared cured is not only a disastrous setback for the individual concerned, it is also the most dependable indication of unsuccessful chemotherapy. Relapse was common after dapsone monotherapy came into use (10): as early as 1950, Erickson noted that, of 33 lepromatous patients who had been treated with disubstituted derivatives of dapsone and had been bacteriologically negative for 12 months, 20 had relapsed within 6–60 months (11).

In 1954, Lowe (12) reported an 11% relapse rate among 148 lepromatous patients discharged as arrested after sulfone treatment. These relapses occurred early, usually within 1 year, and almost always within 2 years, of discharge. Rodriguez (13) observed relapses in 4.4% of 1125 cases who had been negative for periods ranging from 2 months to 10 years.

To minimize relapse, he advocated that sustained treatment of discharged cases be continued for a minimum period of 5 years. Most relapses were occurring in patients who considered themselves completely “cured” and had stopped taking their medicine – hence the growing consensus of opinion among leprologists that treatment should be continued for life to prevent relapse (14). The first aim of MDT being to prevent the emergence of drug-resistant strains of *M. leprae*, the absence of relapses is, so to speak, the litmus test of the effectiveness of chemotherapeutic regimens.

Assessing the frequency of relapses, however, is no easy task, since different definitions are used to describe the phenomenon; this makes comparison difficult. WHO defined a relapsed case as “a patient who successfully completes an adequate course of multidrug therapy, but who subsequently develops new signs and symptoms of the disease either during the surveillance period or thereafter” (15). Among the criteria for relapse are the following (16):

- new skin lesions;
- new activity in previously existing skin lesions;
- bacteriological index (BI) 2+ or more in two sets of skin smears;
- new loss of nerve function;
- histological evidence of relapse in skin or nerve biopsy;
- lepromatous activity in the eye(s).

Some have defined relapse simply as “the reappearance of *Mycobacterium leprae* in skin smears”, while others (10) have referred to “the finding of a new skin lesion with high smear BI-containing solid-staining bacilli, and an histological appearance. Bacilli obtained from a new lesion will multiply in the footpad of mice.”

Since relapses may occur in both PB and MB patients, specific definitions were put forward for each type of the disease. A proposed definition of relapse in a PB patient was “appearance of a new skin lesion or the increase in size of a pre-existing skin lesion, provided there was either strong clinical or definite histopathological evidence (or both) of leprosy in such a lesion” (17). The following seven criteria were proposed for defining relapse in PB leprosy (18): extension of the lesion, infiltration, erythema, occurrence of fresh lesions, pain and tenderness of nerve, new paralysis of muscles, and bacteriological positivity.

While relapse in MB cases is relatively easy to recognize clinically, it may be difficult to distinguish it from reversal reaction occurring some time after therapy is completed (4). In marked contrast to the frequency of relapses following dapsone monotherapy, relapse rates following MDT were considerably lower.

A number of reports on relapses in both PB and MB patients were published; these used different definitions and were based on a number of criteria such as clinical signs, morphological aspects of the bacilli, neural function, and combinations thereof. In spite of the wide variety of definitions, the rates provided in these reports, after revision and standardization by WHO, are minimal, ranging from 2.4 to 8 per 1000 person-years of observation for MB leprosy and from 6.5 to 30 per 1000 person-years for PB leprosy.

In order to assess more precisely the risks of relapse, field trials of MDT regimens were initiated in the early 1980s for MB leprosy in southern India and for PB patients in Indonesia and Malawi. These trials followed the protocols designed by the THELEP (Chemotherapy of Leprosy) Steering Committee, a component of the UNDP/World Bank/WHO Special programme for Research and Training in Tropical Diseases (TDR). Most of the 2241 MB patients recruited in the trial and monitored for several years had had

prolonged dapsone monotherapy before starting on MDT. About 22% were skin smear positive for *M. leprae* at the time of starting the new treatment. Preliminary results indicated a relapse rate of 0.26 per 100 person-years. In the two PB trials, the relapse rate of follow up was 0.65 per 100 person-years after 4 years in Malawi and 0.12 per 100 person-years after 5 years in Indonesia (10).

A decade later, the Leprosy unit at WHO undertook a pilot survey by questionnaire of post-MDT relapses in 17 countries; this provided information on the follow-up of almost 100 000 MB and more than 150 000 PB cases, for a total of some 600 000 person-years of observation. Relapses were few and the relapse rates well below the acceptable level of 1 per 100 person-years, despite most respondents' using a very wide range of criteria to define relapse. (Experts agree that a theoretical relapse rate of 1 per 100 person-years is acceptable for any new regimen; relapses with MDT are far below this, at around 0.1 per 100 person-years or 1 per 1000 person-years.)

Since the information collected in the pilot survey was not considered sufficient for calculating the chances of relapse in individual patients, it was decided to identify programmes that maintain excellent information systems and so could provide information on cohorts of patients observed over a period of time. Twenty-eight such programmes participated, providing information on annual cohorts of patients who began treatment with MDT between 1982 and 1990. The results of this study, covering more than 20 000 MB and 50 000 PB patients, revealed that the risk of relapse was very low: 0.77% for MB and 1.07% for PB, 9 years after stopping MDT. The risk was thus 10 times lower than for dapsone monotherapy. It was therefore postulated that the introduction of MDT had probably prevented close to half a million relapses during the 1980s (10).

Further results from these studies had considerable operational implications. For example, there was strong evidence that 50% of relapses in MB patients occur within the first 3 years of stopping MDT and 75% within 6 years. Among PB patients, 50% of relapses occur within 2 ½ years and 75% within 5 years. Moreover, there were indications that there is no increase over time in the annual risk of relapse in either MB or PB patients. In other words, if there is no relapse within the first 5–6 years, the individual patient's risk of relapsing is negligible. With such a low risk of relapse, and since the majority of relapses occur within a few years of stopping MDT, there seems to be no need for active, long-term, post-MDT follow-up of patients for the sole purpose of detecting relapses (10): patients can be declared "cured" after completion of treatment.

These findings no doubt contributed greatly to convincing all concerned partners, from national leprosy programme managers to NGOs, that MDT represented an enormous advance in the control of leprosy.

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3.3 Technical difficulties in the expansion of MDT

S.K. Noordeen

The widespread implementation and expansion of MDT following the recommendation of the 1981 WHO Study Group depended upon:

- technical experts accepting the scientific rationale and justification for and the recommendations on MDT as defined by the Study Group;
- programme managers and policy-makers of national leprosy programmes accepting the cost and other implications of MDT (at that time there was no assured funding for purchase of MDT drugs);
- donor agencies, including donor NGOs, accepting the financial and other implications, as they would be asked by national leprosy programmes to support the additional costs of MDT.

In order to meet the challenge of the growing failure of leprosy control, the three groups had to interact closely and work towards implementing MDT. The technical experts comprised:

- experts from THELEP and those who interacted closely with them;
- experts who were generally outside the THELEP group, who looked at treatment of leprosy mainly as a dermatological problem and as a result did not fully understand the antibacterial focus of chemotherapy of leprosy; for them, clinical response was the key indicator of successful treatment, and many did not believe that leprosy treatment could be stopped after a finite period, irrespective of the bactericidal activity of MDT drugs.

Of the three groups – technical experts, national policy-makers, donor agencies – who reacted to the recommendations on WHO MDT, it was the donor agencies that were relatively easy to deal with. They could see the great advantage in accelerating leprosy control and reducing the negative image of leprosy through MDT, even if it meant additional costs and human resources inputs. The lead role provided by agencies such as TNF and SMHF encouraged the acceptance of MDT by many others. After extensive internal discussions, ILEP agencies agreed to implement and support MDT, even though one member agency promoted drug combinations other than WHO MDT – Isoprodian[®] – within the ambit of what they could call MDT.

Most national programmes simply accepted what WHO and/or ILEP members recommended without necessarily going into the merits or implications of MDT. This was facilitated by the earlier participation of many national programme managers in the 1981 Study Group itself. In two countries, India and Brazil, with the preponderance of the world's leprosy burden problem, experts discussed at length the issue of implementing MDT. Improving chemotherapy for disease control was already on the agenda in India and preliminary field studies had begun as early as 1979, but serious discussion of MDT began just a few months before the 1981 meeting of the WHO Study Group. This was done through a Working Group on the Eradication of Leprosy, set up by the Government of India in July 1981 under the chairmanship of a renowned scientist, Dr M.S. Swaminathan.

The Working Group's discussions on MDT coincided with those of THELEP and with the 1981 WHO Study Group. Thus, by the time the Government's Working Group published its reports in February 1982, it was able to accept the recommendations of the WHO Study Group (whose report was also published in 1982), with a minor modification to the treatment

of MB leprosy. This modification involved incorporating an additional daily rifampicin dose for the initial 2 weeks of treatment, but was abandoned by the Indian programme in 1990. MDT was also the subject of intense discussion at meetings of the Indian Association of Leprologists (IAL); WHO MDT was discussed in a special seminar of IAL in March 1982, and adopted by the Association's general assembly in November 1983. IAL also introduced a minor modification to the WHO MDT regimen for MB patients, adding an optional 3 weeks of daily rifampicin at the start of treatment.

The situation in Brazil was far more difficult. The national programme was dominated by traditional leprologists who by and large regarded leprosy as a dermatological problem rather than a communicable disease problem. They were not willing simply to accept the recommendations of an external group – even WHO – unless and until they were themselves satisfied with the rationale for and results of WHO MDT. However, a few pilot studies on MDT were carried out and reported favourable results. Even so, it took more than 10 years for the Brazilian national leprosy programme to accept WHO MDT as standard treatment.

The most common problems faced with regard to WHO MDT, particularly in the field, were the following:

- inadequate understanding of the microbiological rationale of MDT and the effectiveness of rifampicin when given at monthly intervals;
- skin discoloration and ichthyosis as a result of clofazimine;
- difficulties in classifying a proportion of patients mainly because of inadequate laboratory services;
- disappointment with the slow decrease of BI in MB patients after MDT;
- slow clinical response in a proportion of patients;
- lack of impact on disability status;
- difficulties in educating patients about what to expect from MDT and why treatment should be stopped after a finite period;
- inadequacy of the health infrastructure to cope with the implementation of MDT in certain areas;
- lack of assured availability of MDT drugs in the long term;
- confusion in the field resulting from the promotion of alternative MDT regimens, including Isoprodian[®], by some agencies.

Most of these problems were resolved by better understanding of the potential of MDT, patient education, increased commitment at all levels, and – principally – experience, in terms of the observed effectiveness of MDT. The extraordinary clinical improvement seen by health workers and patients alike far exceeded their expectations and led to increased enthusiasm and commitment at every level for implementing MDT. MDT came to be seen as a therapeutic revolution and a breakthrough in the hitherto stagnant leprosy control situation.

Appendix 1

WHA44.9 Leprosy

The Forty-fourth World Health Assembly,

Having considered the report of the Director-General on leprosy;

Recalling resolution WHA40.35 and previous resolutions of the Health Assembly and the Executive Board on leprosy;

Noting with satisfaction the significant progress made during the past five years with multidrug therapy for leprosy control and with case-finding in the majority of Member States where leprosy is endemic – progress which has led to reductions in disease prevalence;

Recognizing the substantial and increasing support for leprosy control being provided by nongovernmental and other donor organizations;

Aware of the increasingly high priority accorded by several Member States to the elimination of leprosy as a public health problem;

Further aware of the opportunities to reduce disabilities due to leprosy through early case-detection, multidrug therapy and increased emphasis on managerial capabilities within leprosy control programmes and on disability prevention,

1. DECLARES WHO's commitment to continuing to promote the use of all control measures including multidrug therapy together with case-finding in order to attain the global elimination of leprosy as a public health problem by the year 2000;
2. URGES Member States in which leprosy is endemic:
 - (1) to further increase or maintain their political commitment and give high priority to leprosy control so that the global elimination of leprosy as a public health problem is achieved by the year 2000;
 - (2) to strengthen managerial capabilities within leprosy programmes, particularly at the intermediate level, and to improve training in leprosy for health workers at all levels, including medical students and student nurses;
 - (3) to ensure that coverage of multidrug therapy is maintained at the highest level possible and that patients comply with treatment;
 - (4) to strengthen case-finding activities through various approaches, including health education, community participation and training of health workers;
 - (5) to integrate leprosy control within general health services and provide appropriate social and economic rehabilitation measures as soon as possible in accordance with local realities;
 - (6) to improve national information systems in order to facilitate monitoring and evaluation of the elimination of leprosy;

(7) to coordinate the technical and financial resources made available for leprosy control by international and nongovernmental organizations so that they are utilized in the best way;

3. REQUESTS the Director-General:

(1) to strengthen technical support to Member States for the implementation of multidrug therapy together with case-finding so as to achieve the global elimination of leprosy as a public health problem by the year 2000;

(2) to continue to mobilize and coordinate scientific, technical and additional financial resources for implementing multidrug therapy together with case-finding, disability prevention and social and economic rehabilitation;

(3) to continue to strengthen national capabilities for leprosy control through support for training activities;

(4) to continue to support research for the development of improved drugs, diagnostic tools and vaccines through the Special Programme for Research and Training in Tropical Diseases;

(5) to promote further coordination with Member States and nongovernmental organizations in order to achieve the global elimination of leprosy as a public health problem by the year 2000;

(6) to keep the Executive Board and the Health Assembly informed of the progress made.

