

Chapter 7

Lessons to be learned

H. Sansarricq

7.1 MDT development

Overview

The process that led ultimately to the design of the 1981 Study Group regimens can be viewed as the history – spanning some 40 years - of the modern chemotherapy of leprosy.

Original concepts

The concepts of bacterial resistance to drugs and its prevention, which served as a basis for the Study Group regimens, had been established in the late 1940s and the 1950s from experience with the chemotherapy of tuberculosis.

Two milestones

The first milestone to mark progress in leprosy chemotherapy was the introduction of dapsone in the early 1950s. Considered at the time to be a “miracle drug”, dapsone was used in monotherapy worldwide for about three decades. During the 1960s, however, evidence was steadily accumulating that *M. leprae* resistance to dapsone – an inevitable consequence of the drug’s use as monotherapy – could jeopardize all efforts to control leprosy based on dapsone alone. Nonetheless, it was many years before the importance of this phenomenon was generally accepted.

The second milestone was the introduction of the MDT regimens recommended by the 1981 WHO Study Group.

Experimental advances

For many years, the impossibility of cultivating *M. leprae* in artificial media was an insuperable problem for experimental chemotherapy. However, the mouse footpad model, proposed by Shepard in 1960, which largely overcame the difficulties, was to revolutionize this field of study. Later, the thymectomized–irradiated mouse model, proposed by Rees in 1966, which made possible the detection of *M. leprae* persisters, was used to monitor progress in field trials of the Study Group regimens for MB patients. Other important advances with implications for experimental chemotherapy – though concerned essentially with the relationship between *M. leprae* and its host – came from the Ridley–Jopling spectrum and classification.

Thus, through the meticulous and sustained efforts of numerous scientists and leprosy workers, clinicians and laboratory researchers, complex experimental methods were developed that overcame the considerable difficulties inherent in working with leprosy and its causative organism. In 1981 it finally became possible to design effective and practicable MDT regimens for leprosy control, using the few drugs then available, including rifampicin, which is strongly bactericidal against *M. leprae*.

MDT drugs

Much has already been said, in sections 1.1 and 5.3, about development of the drugs included in the Study Group regimens. Two of the three drugs included in the standard WHO MDT regimens – rifampicin and clofazimine – were developed by Ciba-Geigy (now Novartis, after merger with Sandoz). Of particular importance in relation to the effectiveness of MDT regimens for leprosy is the strong bactericidal activity of rifampicin against *M. leprae*. While the 1981 Study Group regimens were being implemented, a number of new compounds with similar activity against *M. leprae* were identified, meaning that alternative MDT regimens could be developed if necessary (which has already been done with the ROM combination for single-lesion leprosy patients).

THELEP

In 1976, early in the development of the WHO/UNDP/World Bank Special Programme for Research and Training in tropical diseases (TDR), the Scientific Working Group on Chemotherapy of Leprosy – THELEP – was established. THELEP provided a unique opportunity for the leading scientists engaged in research on the chemotherapy of leprosy – most of those responsible for the progress made since the early 1960s – to cooperate, exchange experiences, discuss their findings, and achieve important TDR funding for their work. There can be little doubt that progress in research was facilitated and considerably accelerated by this means.

The first task of THELEP was to organize and sponsor surveys that confirmed the gravity of the problem posed by *M. leprae* resistance to dapsone (see section 6.2).

Moving closer to the Study Group regimens

A failure

Addressing the problem of *M. leprae* resistance to dapsone, the WHO Expert Committee on Leprosy, at its fifth meeting in 1977, recommended the use of combined drug regimens in which rifampicin was to be used in daily doses, because of the fear, prevalent at the time, of toxic side-effects resulting from intermittent doses (see section 6.1, under “New developments”). However, these regimens – and similar regimens recommended by others in the late 1970s – proved impracticable in the field.

An increasing concern

In the later 1970s, as discussed in section 2.1, the anarchic use of rifampicin in leprosy field programmes was causing growing concern about the risk of *M. leprae* developing resistance to this most potent drug at a time when there was no alternative.

The latest steps and the 1981 study group

As explained in section 6.2 (under “Long-term “field” trials at Karigiri and Polambakkam”), in 1979 THELEP designed an experimental regimen – for field trials in MB patients – that was potentially usable for leprosy control. This regimen was based on supervised doses of rifampicin given monthly on two consecutive days. The results of these trials were expected to be available a minimum of 7 years after admission of the first patient, which took place in 1982.

Prompted by the urgent need to end the anarchic use of rifampicin (which implied taking action before the results of the THELEP field trials became available), and in close cooperation with THELEP, LEP convened a WHO Study Group on Chemotherapy of Leprosy for Control Programmes in 1981 (see section 2.1). This Study Group recommended immediate implementation of standard multidrug regimens for MB and PB patients, based on supervised monthly doses of rifampicin and of finite duration.

The respective roles of THELEP and LEP are explained in section 6.1. THELEP was responsible for the development of the MDT regimens for MB and PB patients that were recommended by the 1981 WHO Study Group. LEP took responsibility for catalysing the timely finalization of these regimens, for facilitating their recommendation for immediate implementation, and for securing their official endorsement by WHO. Subsequently, THELEP was responsible for the experimental validation of the Study Group regimens through field trials and publication of the results.

Conclusion

The development and recommendation of the 1981 WHO Study Group regimens provided an excellent example of genuine – and thus productive – cooperation between two WHO programmes dealing with research on chemotherapy of leprosy and technical policy for leprosy control. The regimens were developed and finalized with significant urgency, using the few antileprosy drugs then available (with rifampicin as a crucial component) and based partly on reasonable extrapolations to existing knowledge (see section 2.2).

The fact that these regimens were subsequently to prove not only highly effective but also robust was undoubtedly the result of the high quality of the experimental work on which they were based, complemented by the penetrating intuition of the researchers.

7.2 1982–1990: the first years of MDT implementation

MDT coverage

As described in section 6.1, the introduction of MDT was the top priority for LEP from the time of the Study Group meeting, and the programme spared no effort in putting MDT into practice with the full participation of all concerned. In just a few years, from 1982 to 1985, it was consequently possible to demonstrate, in a number of projects all over the world, that leprosy control based on MDT was entirely feasible, despite certain operational constraints that could not always be resolved.

During the next five years (1986–1990), geographical MDT coverage increased to more than 50% globally (see section 3.1). While this was fairly satisfactory, it is important to recognize that the numbers of cases reported to have been cured by MDT over that period included some patients under long-term dapsone monotherapy.

Although the geographical coverage increased fairly rapidly in the countries of south-east Asia and in western Pacific regions, most African countries and Brazil were rather slow in applying MDT. It is also clear that the countries/areas covered by MDT during these early years of implementation were those where operational conditions were the easiest. Later, in the early 1990s, there was some evidence of “stagnation” in MDT implementation (see under section 6.3), which gave rise to the initiative of resolution WHA 44.9.

Technical aspects

During the 1980s, almost no technical change was made to MDT policy, with the exception of 1987, when the WHO Expert Committee recommended that, for the purposes of MDT, all smear-positive cases should be included in the MB group.

This same decade saw increasing evidence of the robustness of the Study Group MDT regimens.

The reasons for success

The MDT regimens recommended by the 1981 WHO Study Group were in general readily accepted by all concerned patients, communities, health personnel, government authorities, NGOs and other supporting agencies. The reasons for this wide acceptance were that:

- The regimens responded to a felt need.
- Their effectiveness, safety, practicability, and acceptability were rapidly apparent and, in the course of time, convincingly demonstrated.
- In response to the need for complete reorganization of leprosy services required for MDT implementation, all inputs and supports, whether political, technical, or financial, were made available simultaneously – by governments, WHO, international and national NGOs, funding agencies, etc.

Critical factors in the implementation of MDT included the efforts made by the governments concerned in committing themselves to the new technology, and the tremendous work undertaken by national leprosy and health services, and their personnel at all levels, to effect the technical and administrative changes required by the new methods. Of particular importance were the retraining of all staff in the use of the new methods of treatment, and the information and education given to communities on the various practical aspects of MDT.

Conclusion

That all required elements for the successful implementation of MDT (good, practicable technology responding to a felt need, wide acceptability, strong political commitment, adequate technical back-up, and generous financial support) could be made available concomitantly and conveniently.

7.3 1991–2000: elimination strategy

Resolution WHA44.9 and plan for elimination of leprosy as a public health problem

It appears that the concept of eliminating leprosy as a public health problem – that is, identifying and treating with MDT *all* leprosy patients, until prevalence is reduced to a very low level – was first proposed, with a slightly different content, in the WHO Regional Office for the Western Pacific. Noteworthy, too, is that the elimination initiative was recommended by the WHO Executive Board and the World Health Assembly without a WHO Expert Committee meeting, Study Group, or other preparatory step. It may have been felt that a technical meeting was likely to express some reservations about the elimination concept, whereas a WHA resolution proposing a relatively simple objective could be readily adopted and would also have a greater impact on governments and other interested parties.

The elimination strategy included exactly the same technical components as the MDT-based leprosy control strategy, from which it differed in only in two respects – a time limit (the year 2000), and a target (prevalence below 1/10 000 inhabitants). It was rightly expected that these two conditions would ensure both intense commitment and dynamic action on the part of all partners.

Implementation of the elimination strategy

Overview

The period from 1991 to 2000 was marked by comprehensive, intense, and dynamic efforts to solve the problems related to the expansion of MDT coverage to increasingly difficult-to-reach geographical areas or population groups.

In the first years following the adoption of resolution WHA44.9, the response at country level was less positive than had been hoped. In 1994, however, The Nippon Foundation's promise of US\$ 50 million for the purchase of drugs, in addition to technical and operational improvements, notably the leprosy elimination campaigns (LECs), resulted in a marked increase in the extent and efficiency of field activities, with the geographical MDT coverage ultimately reaching 100% in 1997. Sadly, bad news followed shortly afterwards. By 1998, it had become clear that some countries would have to continue their elimination activities beyond 2000.

With the publication of the WHA resolution and the elimination plan, a number of questions and criticisms had been raised by some WHO partners and leprosy experts. During implementation of the elimination strategy, WHO introduced a number of changes and simplifications in technical and operational procedures, with the objective of facilitating and accelerating the elimination plan. These modifications gave rise to further questions and criticisms, notably from ILEP. Over the years, despite the elimination strategy resulting in the cure of millions of leprosy patients, it appears that WHO did not respond in a wholly appropriate manner to such issues, and growing dissent led in the late 1990s to the crisis that has been summarized in section 3.1.

Main elements in the implementation of the elimination strategy

Strong political and financial commitment

It is probably safe to say that resolution WHA44.9 was most welcome in WHO: it responded to the wishes of the Director-General, Dr Nakajima who, as Director of the Regional Office for the Western Pacific, had proposed a similar concept in the late 1980s. Dr Nakajima was also able to secure from The Nippon Foundation – to which he had close ties – important additional financing that, together with other grants, provided the needed impetus to the elimination plan. This close cooperation between WHO and The Nippon Foundation was given prominence, particularly on the occasion of the first and second International Conferences on Leprosy Elimination. By the time of the third International Conference, however, the elimination effort was experiencing some difficulties.

Member associations of ILEP – with the exception of the German Leprosy Relief Association, which was supporting the use of the rifampicin/Isoprodian[®] combination – were in favour of WHO MDT, although they were most insistent on a number of prerequisites for its implementation, particularly in the early years. They had two principal reservations about the elimination plan:

- the definition of “a case” of leprosy recommended by the WHO Expert Committee on Leprosy at its sixth meeting in November 1987, and its implications (see section 5.2);
- fear that an over-optimistic interpretation of the elimination concept would have a negative effect on their fundraising activities.

Nonetheless, they made a most important contribution to the elimination strategy, described in section 5.2.

Simplifications in technology and additional strategies

As discussed in section 3.1, a number of simplifications were introduced in the technical procedures used in the elimination strategy, particularly in many aspects of MDT (regimens, rules for classification of patients, use of skin smears, post-MDT surveillance, etc). These procedural simplifications were made with the ultimate aim of getting more patients treated with MDT. In some instances, the prescribed changes in policy merely reflected simplifications in working methods that had been put into practice by field staff lacking certain skills; a typical example concerned skin smears examinations, which were regarded as extremely important during the 1980s but as unnecessary by the late 1990s.

In an effort to identify “hidden” prevalence, two new strategies were launched in 1995 – the LECs and the Special Action Projects for the Elimination of Leprosy (SAPELs). The LECs proved to be a highly effective tool for the identification of hidden cases provided that new patients were identified by staff of general health services.

Two general strategies that had rightly been considered of crucial importance from the start of MDT implementation received increasing attention during the elimination period. One was the integration of MDT services into general health services; the other was information, education, and communication (IEC) activities aimed at changing attitudes towards leprosy at community level. Even today, further improvement in these two strategies is needed in many countries – probably because this kind of change requires long-term actions, including significant political and administrative efforts, but the period of the elimination strategy has been relatively short.

Programme intensification and monitoring given special attention (see section 3.1)

The WHO global level was substantially reinforced in December 1994 and two successive advisory groups comprising representatives of all parties concerned were monitoring the progress of the elimination plan at all levels (particularly at country level) and proposing solutions for the current operational problems. These advisory groups were assisted by three or four task forces. However, information on operations in some countries, particularly large countries such as Brazil and India, did not always reach WHO by the required deadline.

Position in 2000

More than 12 million leprosy patients were cured as a result of the implementation of MDT-based leprosy control (1982–1990) followed by the elimination strategy (1991–2000). By the end of 2000, however, the overall prevalence for the 12 top endemic countries was still 4.1 per 10 000 inhabitants, and in 1999 it had already been decided to push back the elimination target date to 2005. In addition, 600 000 to 700 000 new cases were still being identified annually worldwide. The following conclusions can be drawn:

- Given the stagnation in MDT implementation in the late 1980s and early 1990s, the elimination strategy was absolutely necessary to reinforce MDT-based leprosy control if the approach was to achieve maximal efficiency.
- The number of patients cured has been increasing over the years and remains a strong *a posteriori* justification for the elimination strategy.
- The fact that the overall prevalence in the 12 most highly endemic countries was still 4.1 per 10 000 inhabitants and up to 700 000 new cases were still being identified annually worldwide was a matter of great concern and one that continues to merit investigation. The paradoxical trend in case detection observed in recent years in some countries, notably India, is particularly deserving of urgent and comprehensive investigation.

7.4 2000 onwards: the final push

While the main elements of the 2000–2005 strategic plan for the final push towards elimination of leprosy remained unchanged, i.e. integration of MDT services into the general health services, and full IEC for communities, new proposals were made for the strengthening or reinforcement of these approaches (see section 3.1). Given that all elements had been already included in the strategy for elimination since 1991 (and to some extent since the late 1980s), it has to be concluded that the progress made in relation to integration and IEC has so far not met the expectations, probably for the reasons explained above.

A recent recommendation from the WHO Technical Advisory Group (TAG) (now responsible for programme intensification and monitoring) is that efforts should be made to persuade national governments to accept “ownership” of their elimination programmes at national and sub-national levels. The lack of this sense of ownership of leprosy activities on the part of some governments may be the result of these activities having been run too exclusively by foreign agencies, with insufficient participation by national authorities. It goes without saying that such situations should be improved.

In 2001, a TAG subgroup recommended that a number of subjects – integration, relapses following 12 months’ MDT in MB patients, ROM, impact of IEC, SAPELs, etc. – be investigated in studies initiated by WHO. From this, it can be inferred that there is some continuing difficulty in evaluating the impact of most of the procedures included in the elimination strategy. It remains urgent to carry out the recommended investigations, especially to reveal the impact of the various simplifications and changes effected during the previous decade.

In 2002, TAG extended the list of procedural simplifications, adding the extended use of accompanied MDT, and a field study on the use of 6 months’ MB MDT regimen for all leprosy patients.

It can be estimated that up to now more than 14 million leprosy cases have been cured. Among the 12 countries that have not reached the elimination target some – notably Brazil and India – are at risk of missing even the 2005 target, largely, it would seem, because integration of leprosy services into general health services continues to be inadequate. If the target date is pushed back yet again, increasing doubts about the feasibility of the elimination plan are likely to arise.

7.5 Current concerns

The elimination strategy is clearly a significant success at national level in most leprosy-endemic countries. However, the time required to reach the elimination prevalence target in some of the most highly endemic countries, notably Brazil and India, and at the sub-national level – where the core of the problem lies – in many countries, remains uncertain.

While the elimination strategy has progressed satisfactorily in many countries, at the global level, since 1998–1999, a crisis has developed between WHO and two of its partners in GAEL – ILEP and TNF – and, more recently, ILA. As reported recently in a so-called independent evaluation, it appears that these three agencies are questioning WHO's leadership not only in implementation of the elimination strategy but also in technical guidance to governments and in research promotion. One of the main contributory factors is quite possibly the critical dependence of leprosy activities on JSIF/SMHF and, to a lesser extent, ILEP as a consequence of the generous support provided by these agencies over the past 25 years or so. In addition, ILEP makes the point that changes and simplifications in the elimination strategy were introduced by WHO without majority agreement from the Organization's partners.

Encouragement and financial support for research related to leprosy were steadily reduced, notably in TDR, probably because the elimination strategy was seen as *the* solution to the leprosy problem. This resulting decline in research is most regrettable, particularly in view of the current uncertainties on the future of the elimination plan. Research in leprosy needs to be stimulated, and it is especially important that the new perspectives provided by the recent sequencing of the *M. leprae* genome should not be missed.

Over the past 25 years or so, the tremendous developments in the WHO leprosy programme – IMMLEP, THELEP, MDT, and the elimination strategy – meant that effective treatment could be made available to all patients everywhere. The Organization's partners made, and continue to make, outstanding contributions, and WHO continues to have a critical role.