Volume 69, Number 3
Printed in the U.S.A.
(ISSN 0148-916X)

INTERNATIONAL JOURNAL OF LEPROSY
and Other Mycobacterial Diseases

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

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VOLUME 69, NUMBER 3 SEPTEMBER 2001

EDITORIAL

Editorial opinions expressed are those of the writers.

Acceptance of WHO/MDT Over the Last 20 Years

Multiple drug therapy (MDT) has been at the core of the leprosy elimination strategy for the last 20 years. Effective in curing the disease and rendering the patient noninfectious after a treatment of relatively short duration, followed by very few relapses and the emergence of drug-resistant strains of *Mycobacterium leprae* having been pre-prescriptions for standard regimens of MDT have resulted in the discharge of millions of patients, which, in statistical terms, has translated 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 Programs," documented evidence on the efficacy of MDT in humans was scarce, or at least incomplete. Clinical field trials at that time were not expected to provide data within a short period of time, since the end point of the trials was the observation of relapses that could occur 5–7 years after completing at least 2 years of treatment. The Study Group was confronted with a dilemma. While there was a lack of field data, and such data could not be made available until many years later, leprosy control was in an awkward predicament. The prevalence of dapsone-resistant strains of *M. leprae* was fast increasing, jeopardizing all efforts made for over 30 years to control the disease by dapsone monotherapy. After much debate, the Group opted for MDT. It was a momentous decision. As evidenced by the subsequent retreat of leprosy, it proved to be correct.

How did WHO manage to enforce, or better, to convince the leprosy world, from governments to nongovernmental organizations (NGOs), from laboratory scientists to field workers, not overlooking the patients, to adopt and accept the MDT standard regimens? How did one succeed in marketing the new strategy of leprosy control in the face of governments confronted with other priorities, indifferent or at times plainly ignorant health workers, scientists skeptical of the premises of the endeavor, clinicians entrenched in their traditional recipes, NGOs pursuing their own parallel agendas, etc.?

For an outside observer, the large acceptance of MDT throughout the last 20 years seems to have resulted from a number of factors. Some of these factors were part of a deliberate plan; others were circumstantial. Not all were operative at the same time, and

they did not necessarily intervene in a logical sequence.

Scientific sanction

The Study Group on the Chemotherapy of Leprosy for Control Programs convened by WHO in 1981 recommended a combination of three drugs—rifampin, dapsone, and clofazimine. The multibacillary (MB) regimen consisted of supervised monthly rifampin and clofazimine, and daily clofazimine and dapsone. Recommendations for paucibacillary (PB) patients were supervised monthly rifampin plus unsupervised daily dapsone.

These recommendations received their ultimate sanction from the WHO Sixth Expert Committee in 1987 as follows: "In view of the very favourable results so far, the Committee strongly endorses the continued use of the standard regimens."

Concurrently, the Medical Commission of ILEP, the International Federation of Anti-Leprosy Associations, forcefully endorsed the WHO recommendations regarding standard MDT regimens. This consensus was important, for ILEP coordinates the activities of 22 NGOs in 16 countries, supporting leprosy control in 104 endemic countries.

Standardization and simplification of procedures

The implementation of MDT was accompanied by modifications in diagnostic and treatment procedures, namely, the standardization of the drug regimens, the classification of patients into two main clinical categories, and a fixed duration for the treatment. This set of measures did not develop all at once. They gradually went on to form what could be called the WHO/MDT package.

Standardization of treatment. The 1982 Study Group recommended strictly standard MDT regimens, differing only according to the clinical type of the patients. Standardization of regimens was no doubt of the utmost importance to speed up the acceptance of MDT. It facilitated the procurement of drugs. It was, at the same time, patient-friendly and convenient for field workers, the more so when later supplied in blister packs (in that respect, one could say that the blister pack was to leprosy elimination what the Ped-o-Jet had been to smallpox eradication).

Case definition and diagnosis. For countless years, the diagnostic criteria and clinical classification of leprosy were the object of heated debate. In the course of time, the decision was made to adopt 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. As to the role of bacteriological examination, the position changed gradually. At the beginning of the period it was emphasized that, "with the introduction of multidrug therapy regimens, the organization of an efficient service for bacteriological examination of skin smears becomes very important" (Study Group, 1981). Still considered as "very important and highly relevant to leprosy control," its poor quality was recognized as "the weakest link in most control programmes" (Sixth Expert Committee, 1987). Ten years later, while the Elimination Action Program was in its final phase, the Seventh Expert Committee (1996) 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." Such a statement ratified a *de facto* situation. What had been tolerance became a prescript.

This simplification no doubt greatly facilitated the life of the field workers, and contributed to making MDT well accepted.

Duration of the treatment. Dapsone monotherapy, used since the 1940s, required more than 5 years of regular treatment to render most, but not all, the lepromatous (MB) patients eligible for discharge. MDT was effective in a short time, possibly within 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 (Study Group 1981, Sixth Expert Committee 1987). The treatment for PB patients was to be given for 6 months.

In 1997, the Seventh Expert Committee 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 misinterpreted as a recommendation to stop all treatments after 12 months.

In view of the impending threat of drug resistance, the recommendation for a standard multiple chemotherapy was well received and widely accepted by a large number of researchers, leprosy control program managers, and NGOs. In some circles, the recommendations met with resistance or at least were accepted with reluctance. At times, academics and private practitioners had a tendency to favor more accurate diagnosis, more sophisticated MDT regimens or treatment of longer duration. The main disadvantage of such options was generally that they made treatment more costly, though not less effective. This resistance gradually ebbed away with the demonstration of the effectiveness of standard MDT, and with the large supply of free drugs provided by or through WHO or the NGOs.

As for reducing the duration of the treatment to 1 year among MB patients, the decision to compel this modification in various countries was criticized by a number of scientists and program managers, who considered it as being based on insufficient evidence and proceeding from an abusive interpretation of the Committee's carefully worded yet ambiguous statement. An open debate on this controversial matter never took place, either at subsequent congresses and meetings, or on the Internet. No doubt, however, it helped to increase the coverage of MDT (while at the same time jamming the prevalence data used in monitoring).

Epidemiological intelligence

Showing how big is a problem is a prerequisite for health authorities at all levels to move. Such is the role of epidemiology.

WHO did not wait for the 1981 recommendations on MDT to foster the collection and retrieval of relevant statistics in leprosy-endemic countries. In 1976, through one university department affiliated with its network of collaborating centers, it sponsored the development of a "Recording and Reporting System for Leprosy Patients (OMSLEP)" which 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 of information necessary to evaluate the progress of control activities."

As early as 1982, steps were taken to make possible the computerization of the system, already surmising that minicomputers (and, later, personal computers) would increasingly come into use in the health services of endemic countries, making it possible to produce reliable, continuously updated information. A workshop was organized in Kuala Lumpur to familiarize leprosy workers from the South-East Asia (SEARO) and the West Pacific (WPRO) regions with the system. This effort was followed by the regular publication of a "Leprosy Epidemiological Bulletin on the Global Evaluation of the Introduction of Multidrug Therapy (1988–1991)," compiling statistics from 168 countries and territories worldwide.

These activities, well timed over successive years, concurred to generate in public authorities and health professionals an awareness of the importance of leprosy as a public health problem. They prepared the ground for the momentous resolution of the World Health Assembly of May 1991 declaring WHO's commitment to global elimination and urging member states to give it full political support.

Elimination as a goal; the World Health Assembly (WHA) 1991 Resolution

At its 44th meeting, the World Health Assembly adopted a resolution (WHA 44.9) proclaiming the goal of attaining the global elimination of leprosy as a public health problem by the year 2000, ". . . elimination being defined as a prevalence rate below 1 case per 10,000 population." This resolution was not immediately accepted by the scientific community, causing some disbelief among a number of leprosy researchers. Neither did it please a number of NGOs, fearing that it could have a negative impact on fund raising. Others were deeply concerned by the fact that the disabling sides of the disease—which on the whole do make of leprosy a major human and public health problem—were apparently overlooked (but disregarding the fact that early detection together with early MDT use is the most ef-

fective way to prevent deformities). Some also felt uncomfortable with the somewhat triumphant accent pervading the whole program, being alarmed by a possible backlash or at least afraid that in the long term it could lead to some "elimination fatigue."

Nonetheless, whatever the reservation or the reluctance, expressed or unspoken, warranted or not (and at times airily brushed aside by WHO officials), the WHA 1991 Resolution provided a formidable booster to the leprosy control activities. It secured the commitment of the national governments. It enrolled the cooperation of managers by using the right, even if at times ambiguous, phraseology. Being target oriented, in terms of global prevalence of 1 per 10,000 population, and time bound (the year 2000), it helped in the planning of resources and in the evaluation of the results.

Deployment of the action program for elimination of leprosy

In the years following the passing of the WHA Resolution, WHO drew up an "Action Programme." It published guidelines, organized meetings, and stimulated national leprosy control services.

The International Conference on the Elimination of Leprosy held in Hanoi in 1994 issued a declaration on the implementation of the Global Plan of Action for the Elimination of Leprosy as a Public Health Problem, ". . . recognising that MDT, the combination of anti-leprosy drugs as recommended by WHO, represents an unparalleled opportunity to master in this millennium the old scourge of humanity.", and urging all concerned ". . . to give top priority for increasing MDT coverage at the highest possible level together with case findings in all endemic areas."

In 1995, the Leprosy Unit at WHO/HQ became a division as the WHO Action Programme for the Elimination of Leprosy (LEP). This decision conferred upon it the authority to provide endemic countries with the appropriate technical support for planning and implementing leprosy programs at the national level. Its activities were periodically reviewed by a "Leprosy Elimination Advisory Committee (LEAG)" composed of external experts. At this point, a major event took place. At the Hanoi Conference, the President of the Sasakawa Memorial Health Foundation pledged to WHO the sum of US$50 million over the next 5 years in order to supply MDT drugs to endemic countries until the end of the millennium. This was a formidable boost. It liberated national governments from the pressure to raise funds for purchasing pharmaceutical products. According to a TDR report, the financial contribution by the Nippon Foundation probably made it possible also for some leprosy NGOs to use their resources previously spent on the buying of MDT drugs for other areas of leprosy control. This generous decision, no doubt, constituted a great incentive for winning governments over to the elimination program.

In subsequent years (1995–1999), the Leprosy Action Program developed intensive activities. The majority of endemic countries reached the prevalence target nationwide. Millions of patients were cured or otherwise discharged. Novel and imaginative strategies were put forward to increase detection, such as SAPEL (Special Action Programmes for the Elimination of Leprosy) directed at populations of difficult access and LEC (Leprosy Elimination Campaigns) set up to strengthen ongoing activities with the help of the local communities. More than 100 special projects (SAPEL) and elimination campaigns (LEC) were launched. While SAPEL yielded relatively few previously undetected cases, LEC led to the detection of several hundred thousand cases. There was a great demand from governments for these short-term, high-gear, costly, vertical projects. In spite of their impact—or perhaps because of it—one may, however, wonder whether they were not sidelining, and to some extent debasing, the customary leprosy control activities, the ones which were supposed to be integrated into the general health services.

In any event, whatever the shortcomings, as far as acceptance of MDT is concerned, the results speak for themselves.

Monitoring

Under the LEAG, a Task Force for the Monitoring and Evaluation of Leprosy (MEEG) was established. The extensive epidemiological data collected throughout the course of the Elimination Program were

tabulated and periodically released in the WHO "Weekly Epidemiological Bulletin" and in annual reports. A number of relevant data were recorded, which have been widely publicized, testifying to the several millions of patients discharged and an over 80% decrease in prevalence. These statistics heralded the brilliant achievements of the activities carried out in the context of the Elimination Program.

Prevalence, a rate based on the total number of patients in the population, was selected as the appropriate index for monitoring the progress of the elimination program. Reflecting the size of the reservoir of infection (the patient with overt disease), it is a proxy indicator for incidence (that is, the rate of appearance of new cases) which could only attest, albeit in the long term, a decline in transmission. There were good practical reasons for this choice. It is simple to compute under field conditions. It provides a single figure as the target, the destination so to speak, to arrive at the scheduled deadline (1 patient for 10,000 population by the year 2000). Prevalence rates, however, have a number of drawbacks. First, compiling the prevalence of registered cases does not provide an estimate of the true prevalence, being dependent upon the completeness of detection. Trends are unsettled by any change in the duration of treatment. A distinction should also be drawn between true decline due to cure or reduction of incidence and administrative decline due to the cleansing of registers.

As the year 2000 deadline approached, managers tended to be enthralled by statistical figures. There was over-reliance on prevalence in following up the progress of the program. One started looking at the prevalence target as the ultimate goal, not realizing that with small numbers, rates become meaningless.

At the same time, the surge in the absolute numbers of cases newly detected can thus be overshadowed by the declining prevalence figures. Too narrow a concern with targets may even produce perverse operational effects by focusing interest on and directing resources toward small populations where the discharge of a couple of patients could lead to a reduction of the prevalence rate large enough to signify the victorious attainment of elimination while overlooking large countries where, in spite of rates below the elimination threshold, thousands of patients remain to be treated.

With treatment duration reduced to 1 year or less, distinctions between prevalence, incidence and case-detection rates are blurred. Already, in not a few countries, point prevalence (that is, the number of patients registered at the end of the year) draws near, or is even below, case detection (that is, the number of cases newly detected during the current year). In the forthcoming years, this figure, by whatever name it goes, will be the indicator to be monitored. In order to derive from it the closest possible estimate of incidence (the ultimate criterion of transmission), the proportion of cases of respectively ancient and recent onset among the newly detected cases will have to be recorded.

Conclusions

WHO/MDT has been at the core of the Leprosy Elimination Program carried out with great success over the last 20 years. MDT is an example of the right technology emerging at the right time to face a sudden challenge. The product of clinical and pharmacological research, it was, so to speak, on standby to combat the emergence of an epidemic of dapsone-resistant *M. leprae*. That, more than anything else, made its success.

WHO was prompt to seize the opportunity. It embodied the recommendations of experts into a package of concurrent measures and a well-formulated strategy in order to make the treatment easy to deliver and well received. Supported by vigorous health marketing efforts, it made for its acceptance.

A commitment of the World Health Assembly, soon followed by the pledge of US$50 million by a major donor for the purchase of drugs, made its worldwide implementation feasible.

By and large, MDT has been extremely well accepted by all partners involved, from the national health authorities and leprosy program managers to donor agencies and NGOs, as well as by those most concerned, i.e., the people affected with the disease. This acceptance was due to a number of

factors, among which the effectiveness and the easy administration of MDT, the decision to wrap its use in a package of simplified procedures, a well-run monitoring system, a vigorous health marketing, the determination and vision displayed in working out novel ways to face unexpected epidemiological or operational situations, the empowerment provided by the authoritative 1991 resolution of the World Health Assembly on elimination and, last but not least, the crucial financial support brought in by nongovernmental donor agencies and foundations.

The achievements in large part matched the expectations, with millions of patients discharged and the prevalence of the disease receding to a considerable extent in many, if not yet all, endemic countries.

These accomplishments, however, were consequent on a compromise. In order to ensure the detection and treatment of the largest possible number of patients, which are the fundamentals of the basic strategy, it was necessary to cut corners and sweep wide while sacrificing the specificity of diagnosis; making do without laboratory support; normalizing the criteria for discharge; using prevalence as the ultimate monitoring instrument; taking some leeway with the issue of integration; running the risk of overlooking reversal reactions; and, finally, relaxing post-discharge surveillance. The detriment was considered minimal when compared with the benefit to be expected from wide coverage. With the drive toward elimination, and as the year 2000 was nearing, flexible recommendations somewhat metamorphosed into rules to be enforced. Latitude became prescripts. This, together with the undisputed and well-publicized success of the program, no doubt reinforced the acceptance of WHO/MDT.

In spite of the remarkable results observed on a global scale, the targets of prevalence have not been achieved by the deadline in all countries. Some of these countries still have a considerable number of patients. This is perhaps not a tragedy. Targets and deadlines are nothing else, after all, than beacons and milestones helpful for managerial purposes. They are not goals *per se*.

In order to complete the program, WHO has set up a strategic plan entitled, "The final push towards elimination 2000–2005." Hopefully, no more corners will have to be cut to wind up the final push. Otherwise, WHO/MDT could fall victim to its acceptance.

Yet, definitively more worrying, the number of new cases detected annually has been remaining stationary, when not increasing, over the last couple of years. This is a great cause for concern. It could call in question the basic epidemiological premises of the current strategy that the patient is the sole reservoir and source of infection of *M. leprae*. It is the challenge to be tackled now, without delay, without whitewashing, and with the same determination and the same vision which characterized the reaction to the emergence of drug resistance 20 years ago.

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