Update/Le point

Leprosy control through multidrug therapy (MDT)*

S.K. Noordeen[1]

Multidrug therapy (MDT) is a major advance in leprosy control and has raised hopes among patients, health workers, and programme managers alike. Where its implementation is vigorous and sustained, the results are extremely gratifying; but problems, both technical and operational, need to be constantly reviewed and solutions found. The opportunities to markedly reduce leprosy in the next decade are immense, but it remains to be seen whether these opportunities are utilized so that leprosy will ultimately be eliminated as a public health problem.

Worldwide situation

Leprosy is a disease of considerable importance in the developing countries of Asia, Africa and Latin America. Apart from being communicable, it also poses challenges in relation to its potential to cause physical deformities and consequent social stigmas. Like many other communicable diseases, it is closely associated with socioeconomic underdevelopment.

The leprosy situation in 1990, as based on registered cases, is shown in Fig. 1 and Table 1. The map indicates that the problem is concentrated in south and south-east Asia, Africa and Latin America where the disease is very unevenly distributed, with registered prevalence rates ranging from <0.1 to ≥3 per 1000 population. Table 1 provides information on registered cases as well as new cases detected, according to WHO regions, for the year 1990. It is clear that in terms of absolute numbers as well as rates the situation with regard to registered cases and new cases is most serious in the WHO South-East Asian Region and, within that region, in India. In terms of concentration of cases, five countries (Brazil, India, Indonesia, Myanmar and Nigeria) contribute to 82% of all registered cases in the world and these countries, together with ten others, contribute to 91% of all cases. Even so, several other countries and parts of others have fairly high rates of prevalence of disease. It should be recognized that the information on registered cases by itself does not fully reflect the true extent of the problem and, where leprosy control programmes and case detection activities are weak, the problem of measuring the magnitude is particularly serious (*1*).

Problems faced by leprosy control prior to 1982

The most important development in leprosy control in recent years is the introduction of multidrug therapy (MDT) in 1982 following the recommendations of a WHO Study Group on Chemotherapy of Leprosy for Control Programmes (*5*). The Study Group took into consideration several problems faced by leprosy programmes including the predominant one of resistance of *Mycobacterium leprae* to dapsone, the most widely used anti-leprosy drug until then.

Drug resistance

A major cause of the setback to leprosy control in the 1970s was the resistance of *M. leprae* to dapsone when the drug was administered as monotherapy. The first report of proven dapsone resistance came from Malaysia in 1964 (*2*). Since then, secondary dapsone resistance has been reported from practically every major leprosy endemic country, often with prevalence rates ranging from 10 to 100 per 1000 (*3*).

Although primary resistance to dapsone had not been reported until 1976, there have been several reports since then identifying primary dapsone resistance as a major problem (*3*).

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[1] Chief Medical Officer, Leprosy Unit, World Health Organization, 1211 Geneva 27, Switzerland.

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Fig. 1. **Prevalence of registered leprosy cases in the world in October 1990.**

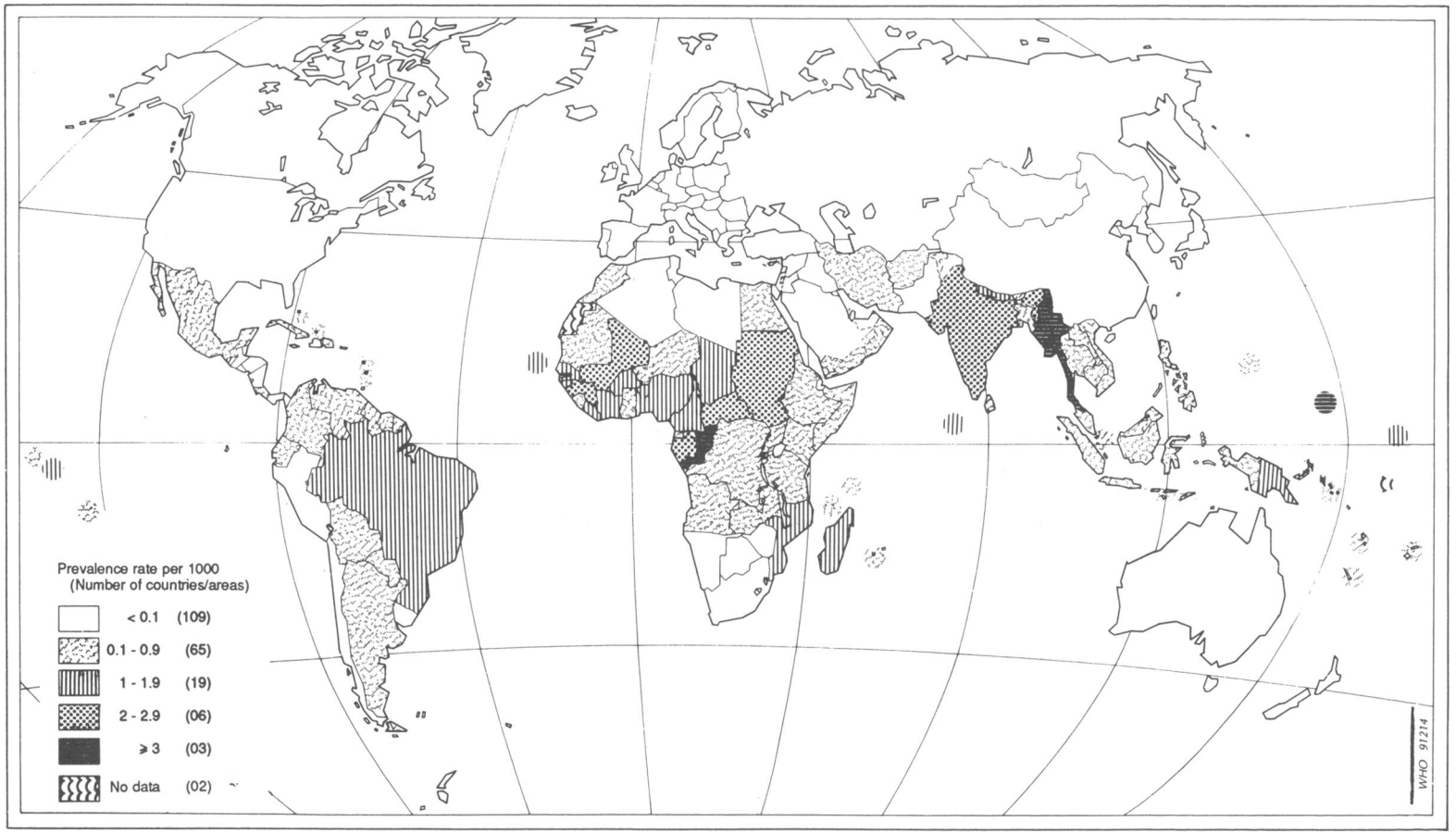

Table 1: **Distribution of registered leprosy cases by WHO Regions, 1990**

WHO Region	Registered cases	Prevalence per 10 000[a]	Percentage of total	New cases detected	Case detection per 10 000[a]
Africa	482 669	9.20	12.91	37 335	0.71
Americas	301 704	4.20	8.08	30 543	0.42
Eastern Mediterranean	99 913	2.60	2.67	6 008	0.15
Europe	7 246	0.10	0.19	87	0.00
S.E. Asia	2 693 104	20.50	72.06	488 285	3.72
Western Pacific	152 739	1.00	4.09	14 103	0.09
Total	3 737 375	7.10	100.00	576 361	1.09

[a] Using the 1990 mid-year population data, from *World population prospects 1988* (*7*).

In addition to resistance against dapsone, drug resistance against other anti-leprosy drugs has also been reported (*3*), particularly when they have been employed in monotherapy. Secondary resistance against rifampicin appears to occur much faster, and although to date only a limited number of resistant strains have been identified, the situation could become very serious if rifampicin is employed singly, or in combination with only dapsone in multibacillary patients. So far, only two cases have been reported of clofazimine resistance, and a few cases of resistance against thioamides, i.e., ethionamide and protionamide.

Microbial persistence

Viable, fully drug-susceptible *M. leprae* that are able to survive for many years in lepromatous patients, despite the presence of bactericidal concentrations of an antileprosy drug, are termed "persisters". In chemotherapy trials supported by the Scientific Working Group on Chemotherapy of Leprosy (THELEP) under the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, persisters have been detected in a small but significant proportion of biopsy specimens from lepromatous patients irrespective of the drug regimen or duration of the treatment (*4*). However, no clear relationship has yet been established between the existence of persisting organisms and the occurrence of relapses, and accumulating evidence from the THELEP-supported field trials suggest that persisters may not pose a serious threat of relapse in patients who are completing multidrug therapy, at least as far as early relapses are concerned. In retrospect, it appears that a very large majority of relapses following dapsone monotherapy in the earlier days were essentially the result of dapsone resistance.

Compliance with dapsone treatment

Compliance with prolonged dapsone monotherapy was a major problem because patients could not see an immediate clinical improvement. The perception of many health workers that dapsone was not sufficiently effective, together with the possibility of relapse, meant that patients had to continue dapsone treatment indefinitely. Further, the negative social attitudes towards leprosy and leprosy patients added to the problem resulting in poor case detection and case-holding of patients.

Public health impact

In the early days of dapsone, it was considered that mass treatment of patients would reduce the reservoir of infection sufficiently to bring about major reductions in the transmission of infection and thus in disease incidence. While reductions in prevalence were possible in well-organized programmes, reductions in incidence were seen only in a very few situations. This failure was due to both a relatively weak technology and its poor application as reflected in low levels of case detection and case-holding.

By the early 1980s it was clear that dapsone was steadily losing its usefulness, owing to drug resistance, and that there was a general lack of enthusiasm for leprosy control in many countries because of the poor results being achieved. Although more potent anti-leprosy drugs were available at that time, the information and guidelines available on how to apply them in a practical way were inadequate. It was in these circumstances that WHO created a Study Group on Chemotherapy of Leprosy for Control Programmes in 1981. This group's recommendations on multidrug therapy are now recognized as an important landmark in the history of leprosy (*5*).

Multidrug therapy

Scientific basis

Increasing dapsone resistance and the availability of better bactericidal drugs against *M. leprae* (such as

rifampicin) in the 1960s made treatment through combinations of drugs a clear possibility. It was realized that while leprosy patients were harbouring very large bacillary populations similar to those with tuberculosis, appropriate chemotherapeutic regimens should be capable of preventing the selection of drug-resistant mutants as well as killing all, or nearly all, drug-sensitive organisms. In such a situation, relapses following completion of chemotherapy could virtually be prevented.

It is estimated that a fully developed lepromatous leprosy patient harbours between 10^{11} and 10^{12} bacilli of *M. leprae*. However, only between 1% and 5% of the organisms are considered viable on the basis of their ability to multiply in the mouse footpad. Thus the mean number of viable organisms in lepromatous leprosy patients is estimated to be about 10^9 or 9 logs. This population consists of several subpopulations of drug-sensitive and naturally drug-resistant strains. Based on the limited evidence available, and also on analogy with tuberculosis, it is estimated that in any wild population of *M. leprae* the number of naturally occurring rifampicin-resistant mutants is about one in 10^7, and the naturally occurring resistant mutants to dapsone, clofazimine and thioamides are about one in 10^6 each. Thus one can expect in a fully developed lepromatous leprosy patient subpopulations of 2 logs of rifampicin-resistant mutants and 3 logs of dapsone, clofazimine and thioamide resistant mutants in addition to about 9 logs of drug-sensitive mutants. In any monotherapy the relevant drug sensitive organisms are killed progressively depending upon the antibacterial activity of the drug, leaving behind the naturally occurring mutants resistant to the drug applied in the monotherapy. It is these unaffected drug-resistant mutants which later multiply and ultimately result in relapses. In multiple drug therapy, this problem is expected to be prevented because the second drug will effectively kill the mutants to the first drug and vice versa. However, it is important to ensure that the drugs selected are bactericidal to the maximum extent possible. In leprosy, while we have one highly bactericidal drug in rifampicin, the other drugs available such as dapsone, clofazimine and thioamides are not as rapidly bactericidal as rifampicin.

Thus it is clear that: (i) all combinations should include rifampicin, (ii) rifampicin should be administered long enough to kill most of the 9 logs of rifampicin-sensitive strains, and (iii) the other drugs should be administered for sufficiently long periods to kill all the naturally occurring rifampicin-resistant mutants. Secondly, the drug regimen should be capable of dealing with persisters, i.e., the small number of drug-sensitive strains that escape killing during the initial period of treatment. Thus, it is the need to effectively kill the rifampicin-resistant mutants and the necessity to eliminate persisters that will determine the duration of treatment.

With regard to the bactericidal activity of rifampicin against *M. leprae*, it is known that a single dose of 600 mg prevents the multiplication of *M. leprae* in the footpad of a normal mouse (*6*). For a similar result, other drugs such as clofazimine, dapsone and thioamides take up to six months. Studies carried out by the Scientific Working Group on Chemotherapy of Leprosy (THELEP), using immune-suppressed mice, suggest that whether rifampicin is administered daily or just once, the initial killing results mainly from the first dose, bringing down the population of rifampicin-sensitive strains from 9 logs to about 4 logs of possible persisters, which are too few to give rise to rifampicin-resistant mutants later on (*4*). Therefore, when lepromatous patients are treated with just rifampicin, the risk of acquired resistance comes mainly from the 2 logs of naturally occurring rifampicin-resistant mutants. Although theoretically just one additional drug should be sufficient to deal with them, two additional drugs are generally considered necessary because of (i) the existence to some extent of dapsone resistance, and (ii) the relatively slow action of the other drugs. Although there are three effective drugs available for this purpose (dapsone, clofazimine, and ethionamide/protionamide), in practice ethionamide/protionamide is not recommended because of toxicity, particularly to the liver, when administered along with rifampicin. This leaves only dapsone and clofazimine as drugs for combination with rifampicin.

The problem of antibacterial treatment of paucibacillary leprosy is somewhat less complicated as the bacterial load is estimated to be less than 6 logs of acid-fast bacilli. The selection of drug-resistant mutants in this population is extremely unlikely and therefore 6 doses of monthly rifampicin should be sufficient to kill the organisms. However, there may be problems due to primary drug resistance, misclassification, and incorrect bacterial assessment. Thus, a second drug along with rifampicin, such as dapsone, will be necessary for the treatment of paucibacillary leprosy.

Recommendations of the WHO Study Group

The recommended standard regimen for *paucibacillary* leprosy is rifampicin 600 mg once a month for six months, plus dapsone 100 mg daily for six months. The administration of rifampicin should invariably be fully supervised, but dapsone may be given unsupervised.

The recommended standard regimen for *multibacillary* leprosy is rifampicin 600 mg once a month, supervised; plus dapsone 100 mg daily, self-administered; plus clofazimine 300 mg once a month, supervised, and 50 mg daily, self-administered.

It should be realized that the Study Group, which comprised scientists researching on leprosy chemotherapy and programme managers who were ready to implement any new treatment in leprosy control programmes, made these recommendations under the special circumstances as indicated earlier. In spite of this and the urgent need to introduce MDT as soon as possible, several questions were raised in the field including those relating to how well the recommended regimens had been tested, how applicable they were under field conditions, and how cost-effective they were. At the same time, a number of leprosy control programmes started initiating limited applications of the WHO/MDT. After two or three years, the initial information about safety and to some extent efficacy was highly favourable, with the result that larger and larger applications became possible. The net result was that by the end of 1990, close to 3.3 million leprosy patients had completed or were undergoing multidrug therapy in nearly one hundred leprosy endemic countries.

The Scientific Working Group on Chemotherapy of Leprosy (THELEP) had an important role in the development of the WHO recommendations and was constantly involved in the evolution of MDT. In 1982, THELEP set up in South India two large-scale field trials among multibacillary patients to validate the recommended regimen as well as another slightly modified regimen. The two trial sites together included 2224 multibacillary patients. During treatment, the average clinical attendance for treatment was between 90% and 93%, and for follow-up it varied between 80% and 90%. The initial status of these 2224 patients indicated that a majority of them were skin smear negative as a result of past treatment with dapsone. During the trial some side-effects were reported, the most common being discoloration due to clofazimine. However, health workers could explain to patients that this was a temporary phenomenon which would disappear once the treatment was stopped. It was therefore not a serious problem for the treatment to be acceptable.

The most important findings expected of the field trials were concerned with relapses after stopping treatment. Among the initially smear-negative patients there was not one case of relapse, based on the accumulated experience of about 7000 patient-years of follow-up observation. In the initially smear positive patients also there was no case of relapse, based on 2000 patient-years of follow-up observation. Thus, more than 9000 patient-years of follow-up spread over four to six and a half years after completion of treatment in over 2000 multibacillary patients showed no case of relapse until the end of 1990. Under dapsone monotherapy a similar situation would have resulted in about 180 relapses in the same part of India. Multidrug therapy, in thus averting a substantial number of relapses, provides more effective leprosy control.

A review by WHO of the implementation of MDT in routine leprosy control programmes in several countries has shown similar results. In routine programmes also the side-effects have been infrequent and clofazimine discoloration was generally acceptable. Regularity of attendance for treatment has also been high, often over 80%. Based on over 85 000 paucibacillary and 22 000 multibacillary patients, it has been shown that the relapse rate was <0.10% in paucibacillary and <0.06% per year in multibacillary leprosy. The value of MDT has therefore been established for leprosy control beyond any doubt.

Progress with implementation

The coverage of leprosy patients with MDT has rapidly increased over the past few years to reach, by October 1990, 55.7% of the total registered cases. The increasing acceptability of MDT among national health services and leprosy patients themselves is due to (*a*) the fixed and relatively short duration of treatment; (*b*) the low-level of toxicity and treatment-related side-effects; (*c*) the very low relapse rates following completion of treatment; (*d*) the high level of acceptance of clofazimine in spite of the discoloration it produces; and (*e*) a significant reduction in the frequency and severity of ENL (erythema nodosum leprosum) reactions. One more advantage, following implementation of MDT, is the considerable increase in the proportion of cases presenting themselves at an early stage of the disease. Consequently this has contributed to a reduction in the number and degree of deformities among new cases as well as increased compliance of patients with the treatment.

The progress over the last four years (1986–90) with MDT is shown in Table 2. Although the global coverage has reached an encouraging level of over 55% of registered cases, this is very unevenly distributed. Coverage by WHO regions, as shown in Table 3, is high in the South-East Asian and Western Pacific regions and quite low in the African and American regions. Even within each region there are considerable variations between countries (Table 4). Overall, of the 93 leprosy endemic

Table 2: **Progress of MDT coverage, 1986–90**

	October 1986	October 1987	October 1988	October 1989	October 1990
Registered cases (× 1000)	5341	5078	4908	3866	3737
No. of cases on MDT	468 222	1 318 964	1 604 927	1 751 903	2 080 998
% of total cases on MDT	8.77	26.00	32.70	45.32	55.68
Cumulative total of cases who completed MDT	93 216	515 144	627 919	853 706	1 204 821

Table 3: **MDT coverage by WHO Region, October 1990**

WHO Region	Registered cases	MDT coverage (%)	Completed MDT
Africa	482 669	18.37	102 552
Americas	301 704	23.75	23 114
Eastern Mediterranean	99 913	38.67	17 177
Europe	7 246	49.72	238
S.E. Asia	2 693 104	66.15	1 020 453
Western Pacific	152 739	63.40	41 287
Total	3 737 375	55.68	1 204 821

Table 4: **Number of countries with a prevalence rate of at least 1 per 10 000 population in WHO Regions, by percentage MDT coverage**

MDT coverage	WHO Regions[a]						
	AFR	AMR	EMR	EUR	SEAR	WPR	Total
>76%	8	12	3	0	4	12	39
51–75%	7	2	1	0	3	3	16
26–50%	4	4	0	0	2	2	12
11–25%	8	1	3	0	0	1	13
1–10%	10	0	1	0	0		11
No information	1	0	1	0	0		2
Total	38	19	9	0	9	18	93

[a] AFR = Africa; AMR = Americas; EMR = Eastern Mediterranean; EUR = Europe; SEAR = South-East Asia; and WPR = Western Pacific.

countries with a prevalence of at least 1 per 10 000 population, 38 countries have poor MDT coverage of less than 50% of their registered cases. Only 39 of the 93 countries have a coverage of more than 75% of their registered cases. This calls for considerable additional attention in countries with poor coverage.

The major problems in such countries appear to be more operational, administrative and financial than technical, in spite of the recognition of the overall advantages. The experience in successful countries clearly indicates MDT to have contributed to (*a*) increased treatment compliance among patients; (*b*) increased voluntary self-reporting, particularly of early disease; (*c*) better motivation of health workers; and (*d*) substantial additional community support as a result of the positive image of MDT as effective technology. However, countries with relatively poor performance with MDT perceive several operational and related problems. These include:

— the inability to increase the priority for leprosy in some countries because of other pressing health needs;
— poor health infrastructure to cope with MDT;
— inadequate resources particularly for drugs;
— absence of a proper plan of action to implement MDT;
— inadequate training of health workers;

— lack of laboratory facilities for skin smear examinations;
— poor referral facilities to deal with complications; and
— insufficient education of patients about what to expect from MDT so that when the time comes for stopping treatment, the decision would be acceptable to them.

Future prospects

The increasing political commitment in many countries to deal with leprosy effectively, which is the result of a good appreciation of the value of multidrug therapy and increasing international cooperation, both bilateral and multilateral, could very well lead to a reduction of the leprosy case-load globally by as much as 90% in the next ten years. However, despite this anticipated major reduction in prevalence, other problems will remain for a long time such as disabilities among old cured patients and a continued, albeit reduced, incidence of new disease arising from infections caught several years earlier. Hence, apart from investing heavily in efforts to reduce leprosy prevalence through MDT, there is a need to plan future leprosy control programmes within primary health care, including early detection, treatment, as well as disability prevention and management.

References

1. **Noordeen, S.K. & Lopez Bravo, L.** The world leprosy situation. *World health statistics quarterly*, **39**: 122–128 (1986).
2. **Pettit, J.H.S & Rees, R.J.W.** Sulphone resistance in leprosy: an experimental and clinical study. *Lancet*, **2**: 673–674 (1964).
3. **Ji Baohong**. Drug resistance in leprosy: a review. *Leprosy review*, **56**: 265–278 (1985).
4. **Sub-committee on clinical trials of the Chemotherapy of Leprosy (THELEP) Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases**. Persisting *M. leprae* among THELEP trial patients in Bamako and Chingleput. *Leprosy review*, **58**: 325–337 (1987).
5. WHO Technical Report Series, No. 675, 1982 (*Chemotherapy of leprosy for control programmes*: report of a WHO Study Group).
6. **Levy, L.** Application of the mouse footpad technique in immunologically normal mice in support of clinical drug trials, and a review of earlier clinical drug trials in lepromatous leprosy. *International journal of leprosy*, **55**: 823–829 (1987).
7. **United Nations**. *World population prospects 1988*. New York, 1989.