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RISK OF RELAPSE IN LEPROSY

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RISK OF RELAPSE IN LEPROSY**SUMMARY**

Until the introduction by WHO of the standard regimens using multidrug therapy (MDT) for the treatment of leprosy, there was a general unwillingness to release patients from treatment. This was mainly due to the high risk of relapse after dapsone monotherapy. After almost a decade of MDT implementation and after releasing more than 4 million patients, it was necessary for WHO to review the risk of relapse following WHO-recommended MDT. The results of this study, carried out on more than 20 000 MB and 50 000 PB patients, revealed that the risk of relapse is very low, 0.77% for MB and 1.07% for PB, nine years after stopping MDT. In comparison to dapsone monotherapy, the risk is 10-times lower. Thus, over the last decade, MDT implementation has probably prevented close to half-a-million relapses.

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RISK OF RELAPSE IN LEPROSY

1. INTRODUCTION

The most natural expectation of any individual who is sick is to be completely cured of the illness with treatment and have minimal or no risk of relapse. However, for centuries persons suffering from leprosy were unable to obtain this simple assurance, initially because of the non-availability of treatment, and later due to the high risk of relapse with the then available treatment. Leprosy remained an incurable disease in the minds of its sufferers, the leprosy workers and the society.

The discovery of sulphones, notably dapsone, in the early 1940s had brought a new hope to leprosy patients. However, this hope proved to be short-lived, and as early as 1950 reports of "failures" with dapsone monotherapy began to appear in the literature.^(8,9,10,12,19,21,29,32,37) Some studies reported the proportion of patients relapsing to be as high as 30%. Others, using person-years of observation, cited relapse rates as high as 3 per 100 person-years of observation.^(3,13,17,18,22,32,35) One recent study, using a life-table method, observed a cumulative risk of relapse of 40% over a 30-year period of observation.⁽⁷⁾

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2. DEFINITION OF RELAPSE

The published literature on relapse often uses different definitions, and this makes comparisons difficult.

The Guide to Leprosy Control (WHO, 1988) defines relapse 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..."⁽⁴⁰⁾

Beck-Bleumink lists several criteria for relapse⁽⁴¹⁾, which include:

- a) new skin lesions;
- b) new activity in previously existing skin lesions;
- c) Bacteriological Index (BI) 2+ or more in two sets of skin smears;
- d) new nerve function loss;
- e) histological evidence of relapse in skin or nerve biopsy;
- f) lepromatous activity in the eye(s).

Others have defined relapse simply as "the reappearance of *Mycobacterium leprae* in skin smears", while some have suggested "the finding of a new skin lesion with a high smear BI-containing solid-staining bacilli, and an histological appearance. Bacilli obtained from a new lesion will multiply in the footpads of mice."^(2,20,36)

Boerrigter *et al*⁽⁹⁾ defined relapse in PB patients as "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."

Pandian *et al*⁽²²⁾ included seven criteria for defining relapse in PB: "extension of the lesion, infiltration, erythema, occurrence of fresh lesions, pain and tenderness of nerve, new paralysis of muscles and bacteriological positivity."

The Sixth WHO Expert Committee on Leprosy (1988) agreed that, "relapse in MB cases is relatively easy to recognize clinically", while "relapse in PB cases may be difficult to distinguish clinically from reversal reaction occurring some time after therapy is completed."⁽³⁹⁾

3. REASONS FOR RELAPSE

3.1 Drug resistance

The results of formal surveys conducted by WHO, through the Special Programme for Research and Training in Tropical Diseases (TDR), and studies carried out elsewhere, showed that the prevalence and incidence of dapsone resistance was increasing alarmingly in several areas. It became clear that the

treatment of leprosy with dapsone alone could not prevent the development of drug resistance, even if patient compliance significantly improved, and eventually as many as 50% of MB patients could relapse with drug-resistant *M. leprae*.^(14,24,25,26,27,28,37,38)

3.2 Persistence of *M. leprae*

The finding of *M. leprae* in biopsy material of patients considered to be "cured" after prolonged dapsone monotherapy led to the belief that *M. leprae* may remain viable in some immunologically favourable sites. One of the reasons for this was considered as non-penetration of dapsone into these sites.^(6,15,34)

However, it was demonstrated that the persistence of viable drug-sensitive *M. leprae* cannot be due to inadequate tissue penetration of dapsone or any other anti-leprosy drug. It was postulated that persisters are physiologically dormant bacilli and can thus escape the action of drugs.⁽¹⁾

Clinical trials carried out by THELEP (the Scientific Working Group on Chemotherapy of Leprosy, now known under TDR as "THEMYC") at Bamako and Chingleput, concluded that persisters could be present in about 10% of MB patients and were not killed by any of the

drug combinations employed in the trials. An important observation in these trials was that the proportion of persisters may be higher in patients with a higher population of *M. leprae* and may lead to greater risk of relapse or treatment failure.⁽³¹⁾

4. RELAPSES AFTER MDT

4.1 Published data

In comparison with dapsone monotherapy, the data on relapses after MDT (both WHO-recommended⁽³²⁾ and other modified MDT regimens) are still very limited, especially for MB leprosy, and everything published in the last decade has displayed similar weaknesses in definitions and methodology.

This could perhaps be best illustrated by summarizing some of the more important publications.

**Table 1: Relapse rates after MDT in PB leprosy in different studies
(Revised)**

Authors	No. of patients	Relapse per 100 person-years	Definition of Relapse
Boerrigter et al ⁽⁵⁾	484	0.65	New skin lesions or increase in size of old lesions
van Brakel et al ⁽³³⁾	555	0.73	Return of active disease
Grugni et al ⁽¹¹⁾	1 509	1.8	New lesions, extension, thickening, erythema in old lesions, thickened nerves, new paralysis, reversal reaction
Katoch et al ⁽¹⁶⁾	70	3.0	Gradual reappearance of activity
Pattyn et al ⁽²³⁾	60	1.5	Return of histological lesions
Reddy et al ⁽³⁰⁾	92	1.7	Reappearance of the disease, reversal reaction

**Table 2: Relapse rates after MDT in MB leprosy in different studies
(Revised)**

Authors	No. of patients	Relapse per 100 person-years	Definition of relapse
van Brakel et al ⁽³³⁾	372	0.8	Return of active disease, including neuritis, nerve function loss, iritis, reversal reaction, new lesions, positive smear, active lesion, erythema
Beck-Bicuminck ⁽⁴⁾	2 379	0.24	BI of 2 or more in one or more sites, confirmed by a second set of skin smears, leprosy bacilli in skin or nerve biopsy, new nerve function loss, active skin lesion
Marchoux Chemotherapy Study Group ⁽²⁰⁾	44	0.8	BI increase by at least 2+ at any site, confirmed by re-examination, definite new lesions with BI greater than any pre-existing lesion
WHO Expert Committee ⁽³⁹⁾ TRS 768	9 000	0.02	Not specified

The data presented in Tables 1 and 2 have been slightly revised with respect to relapse rate/100 person-years of follow-up in order to standardize the rates for easy comparison.

The following procedure was used:

- i) review of the original publication;
- ii) use as numerator of the number of relapses as agreed by the authors in the publication;
- iii) wherever possible, use as denominator of the number of patients under observation multiplied by the average duration of follow-up. This average time is estimated by taking into account the date of intake, the duration of treatment and the date of observation.

While this method is approximate, it gives a better idea of the risk of relapsing.

4.2 THELEP (THEMYC) trials

4.2.1 MB leprosy

Two field trials of WHO-recommended MDT regimens in MB leprosy patients were initiated during 1982-83 at Polambakkam and Karigiri in South India.

Most of these patients had had prolonged dapsone monotherapy before

starting on MDT. About 22% of these were skin-smear BI-positive at the time of starting the new treatment.

Of the 2241 initially recruited patients, 1748 (78%) continued to be followed-up until the end of 1993.

The trial protocol defined relapse as:

- a) evidence of clinical activity in skin lesions with a positive BI; and/or
- b) positive bacteriological finding when repeated twice, without clinical evidence of activity of the disease.

The total duration of follow-up amounts to approximately 15 000 person-years of observation. To date, only four MB relapses have been identified, giving a relapse rate of 0.26/1000 person-years.

Two of these relapses were independently confirmed. The results of mouse footpad inoculation carried out for viability and drug susceptibility for one patient showed *M. leprae* susceptible to all three drugs (dapsone, clofazimine and rifampicin); results for the second relapse are awaited.

4.2.2 PB leprosy

THELEP-supported field trials of WHO-recommended MDT regimen in PB leprosy were conducted in Karonga, Malawi, and

South Sulawesi, Indonesia.

The Malawi trial recruited 503 new PB leprosy patients, of whom 484 were followed for about 4 years (about 2000 person-years). During this period, 12 relapses were detected, giving a relapse rate of 0.65/100 person years.

The Indonesian trial recruited 565 new PB leprosy patients, of whom 471 were followed for about 5 years (about 2500 person-years). During this period, 3 relapses were detected, giving a relapse rate of 0.12/100 person-years.

4.2.3 Pilot Questionnaire Survey on relapse after MDT

In the latter part of 1991, the Leprosy Unit, WHO, had undertaken a questionnaire survey of post-MDT relapses. The objective was to assess the extent of the problem, if any, from a variety of programmes. It was hoped that the responses would provide information on a sufficiently large number of patients completing a reasonable period of post-MDT surveillance. A simple questionnaire was sent to 30 individuals from 17 countries and included about equal proportions of National Programme Managers, State/District Programme Managers and Project Managers from Referral Centres.

The information provided by the 26 programmes who completed the questionnaire is summarized in Table 3.

**Table 3: The first WHO Post-MDT questionnaire survey
Summarized results**

Type of leprosy	No. of patients	No. of relapses	Person-years	Relapse rate per 100 person-years
MB	92 194	467	199 939	0.23
PB	158 182	625	409 508	0.15

The response to the questionnaire and the preliminary results were very encouraging. The relapses were very few and the relapse rates were well below the acceptable level of 1 per 100 person-years, in spite of most respondents using a very wide range of criteria to define a case of relapse in their programmes.

5. EXTENDED QUESTIONNAIRE SURVEY ON POST-MDT RELAPSES

Information collected in the pilot survey was not considered appropriate for calculating the probability/risk of relapsing for an individual patient. Therefore, it was decided to identify those programmes which maintain excellent information systems and which could provide information on cohorts of patients observed over a period of time:

5.1 Methodology

The extended post-MDT questionnaire survey received information from 28 selected programmes. The respondents

completed a set of nine detailed forms which included information on annual cohorts of patients who began treatment with MDT between 1982 and 1990. The questionnaire included information on each cohort observed during 1984-1992 for MB and 1982-1992 for PB, and relapses diagnosed during this period. This entailed a great deal of meticulous and laborious work by the respondents and their colleagues, who had to collate the information required from individual patient registers.

5.2 Results

The risk of relapse for MB and PB cases is shown in Tables 4 and 5 respectively.

5.2.1 MB leprosy

A total of 20 141 patients were observed during the period 1984-1992, of whom 67 were diagnosed as relapses, the mean and median time for relapse being 3.42 and 3.00 years respectively.

Table 4: Cumulative risk of relapse: MB

Years of follow-up	No. of patients	Relapses	Annual rate of relapse %	S.D.*	Cumulative risk of relapse %	S.D.*
1	20 141	6	0.03	±0.01	0.03	0.01
2	16 649	19	0.11	±0.03	0.14	0.04
3	12 180	14	0.12	±0.03	0.26	0.07
4	10 225	14	0.14	±0.04	0.40	0.10
5	7 457	1	0.01	±0.01	0.41	0.12
6	5 045	7	0.14	±0.05	0.55	0.12
7	3 689	4	0.11	±0.05	0.66	0.22
8	2 569	1	0.04	±0.04	0.70	0.27
9	1 414	1	0.07	±0.07	0.77	0.36

* S.D. = Standard Deviation

Table 5 : Cumulative risk of relapse: PB

Years of follow-up	No. of patients	Relapses	Annual rate of relapse %	S.D.*	Cumulative risk of relapse %	S.D.*
1	51 553	46	0.09	±0.01	0.09	0.01
2	41 880	94	0.22	±0.02	0.31	0.05
3	33 144	106	0.32	±0.03	0.63	0.08
4	25 735	31	0.12	±0.02	0.75	0.10
5	15 729	20	0.13	±0.03	0.88	0.23
6	7 373	8	0.11	±0.04	0.99	0.17
7	3 035	0	0.00	±0.00	0.99	0.23
8	1 320	1	0.08	±0.08	1.07	0.31
9	612	0	0.00	±0.00	1.07	0.46

* S.D. = Standard Deviation

5.2.2 PB leprosy

A total of 51 553 patients were observed during the period 1982-1992 of whom 306 were diagnosed as relapses, the mean and median time for relapse being 2.75 and 2.00 years respectively.

The cumulative risk of relapse for MB and PB leprosy is shown in a graphic form in Fig. 1. The comparative relapse risk for MB patients when compared with dapsone is shown in Fig. 2.

Figure 1: POST-MDT: CUMULATIVE RELAPSE RISK

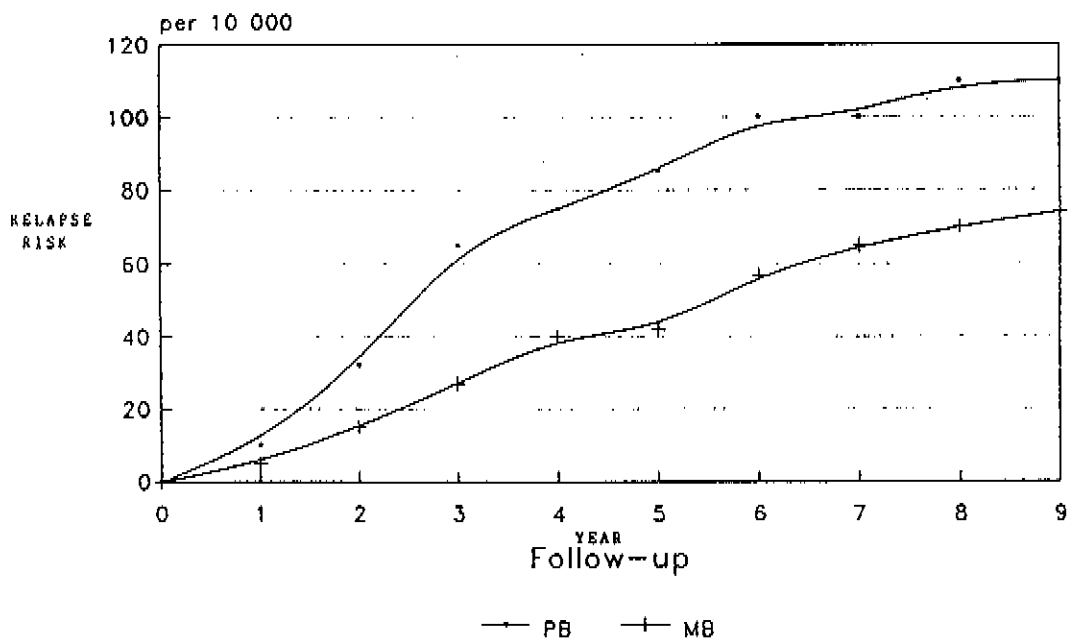
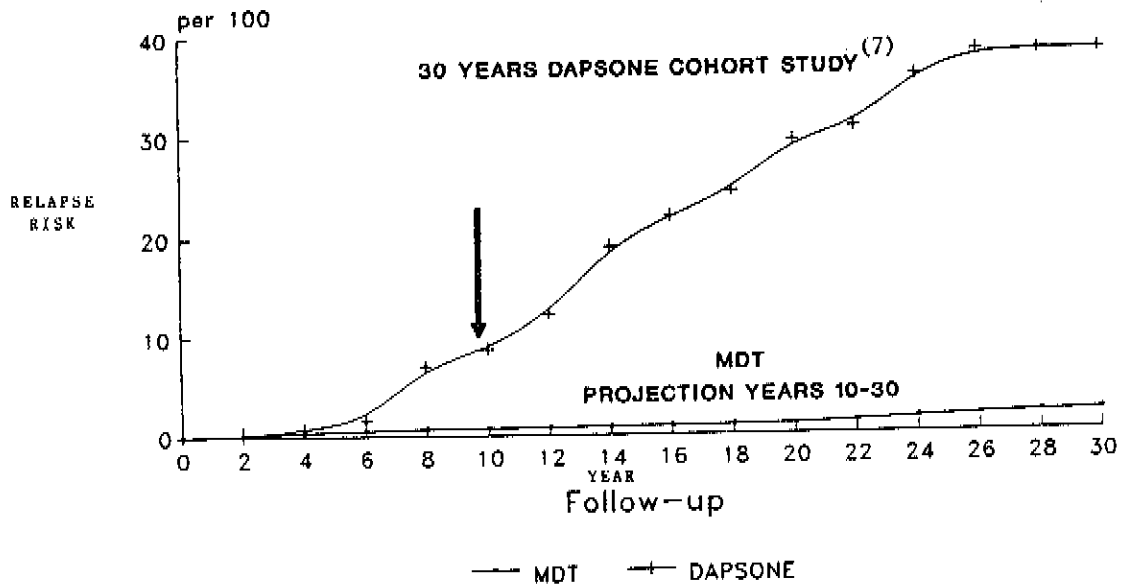


Figure 2: COMPARATIVE RELAPSE RISKS - MB PATIENTS



6. DISCUSSION

The study covers a wide range of patients and conditions with variations in:

- (a) the definition of relapse;
- (b) the proportions of previously dapsone-treated and new, untreated patients;
- (c) the range of skin-smear positivity among MB patients;
- (d) the different proportions of self-reporting and actively followed-up patients;

- (e) the different durations of follow-up.

However in spite of these limitations, the results to a great extent reflect the reality in the field. Most programmes have decided to over-diagnose relapse, with broad criteria defining relapse in the field. This is justifiable in the interests of the patients as the methods available to confirm relapses in MB, through mouse footpad studies, and PB, through therapeutic tests with corticosteroids, are expensive and time-consuming.

7. CONCLUSIONS

- (a) The most significant result is that the risk of relapse is very low, both for MB and PB patients, after completion of MDT.

If we assume that all the biases and limitations which could possibly affect the results of this study were also, to a large extent, applicable to studies on relapses occurring after monotherapy with dapsone, then we find that the risk of relapsing with MDT is at least 10 times less than with dapsone monotherapy.

- (b) There is strong evidence that in MB patients, 50% of relapses occur within the first three years after stopping MDT, and 75% within 6 years. Among PB patients, 50% of relapses occur within 2½ years and 75% of relapses within 5 years.

Moreover, there are indications that in both MB and PB patients the annual risk of relapse does not increase over time. In other words, if in an individual patient the disease does not relapse within the first 5-6 years, then his/her risk of relapsing is negligible.

- (c) With such a low risk for relapse and since the majority occur within a few years after stopping MDT, there is definitely no need to have long-term active post-MDT surveillance of patients for the purpose of detecting relapse. In other words, patients can be declared "cured" after completion of treatment.
- (d) The protective effect of MDT in preventing post-treatment relapses as compared to dapsone is more than 90%. In other words, it can be estimated that the introduction of MDT has probably prevented close to half a million relapses during the last decade.

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