INTERNATIONAL JOURNAL OF LEPROSY

Volume 67, Number 4
Printed in the U.S.A.
(ISSN 0148-916X)

INTERNATIONAL JOURNAL OF LEPROSY
and Other Mycobacterial Diseases

VOLUME 67, NUMBER 4 DECEMBER 1999

Studies on Risk of Leprosy Relapses in China: Relapses After Treatment with Dapsone Monotherapy[1]

Xiang-Sheng Chen, Wen-Zhong Li, Cheng Jiang, and Gan-Yun Ye[2]

The organized leprosy control program was launched in China in the mid-1950s. Dapsone (DDS) administration as monotherapy remained the mainstay of leprosy treatment until 1986 when the World Health Organization-recommended multidrug therapy (WHO/MDT) was introduced nationwide. However, many of the patients reaching clinical cure were still kept on maintenance therapy with regular or irregular dapsone 50–100 mg daily for 5–10 years for multibacillary (MB) patients and 2–5 years for paucibacillary (PB) patients, and even in some patients the treatment duration was life-long. Between 1949 and 1997, 472,771 leprosy patients were detected of whom approximately 80% had been treated with DDS monotherapy, 11% with MDT recommended by WHO, 3.3% with other regimens, mainly including various durations of dapsone plus rifampin, during 1979–1984 in some areas, and the remaining 5.7% of the patients had never received any formal treatment. Since 1949 a total of more than 310,000 patients have been treated with DDS monotherapy and declared as clinically cured. The patients treated with DDS were declared as clinically cured when they achieved clinical, bacterial index and histopathological negativity. For the purpose of evaluating the long-term efficiency of DDS monotherapy and providing some light on the surveillance and management for the patients cured by DDS monotherapy, relapses among the patients who had been cured by DDS monotherapy and followed up for up to 40 years are reported as follows.

MATERIALS AND METHODS

This study is part of a large project covering the whole of China for the purpose of establishing a national system for the epidemiological study and surveillance of leprosy. Based upon this project, the National System for Leprosy Surveillance was initiated in 1989 by the Ministry of Public Health and established in the National Center for STD and Leprosy Control located in Nanjing. Excluding three nonendemic areas (Beijing, Inner Mongolia and Shanxi) as

[1]Received for publication on 18 June 1999. Accepted for publication on 9 September 1999.

[2]X.-S. Chen, M.D.; W.-Z. Li, M.D.; C. Jiang, M.D.; G.-Y. Ye, M.D., Professor, Department for Leprosy Research, Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center for STD and Leprosy Control of China, 12 Jiangwangmiao Street, Nanjing 210042, China.

Reprint requests to Dr. Chen at the above address or FAX: 86-25-541-4477; e-mail: epicams@jlonline.com

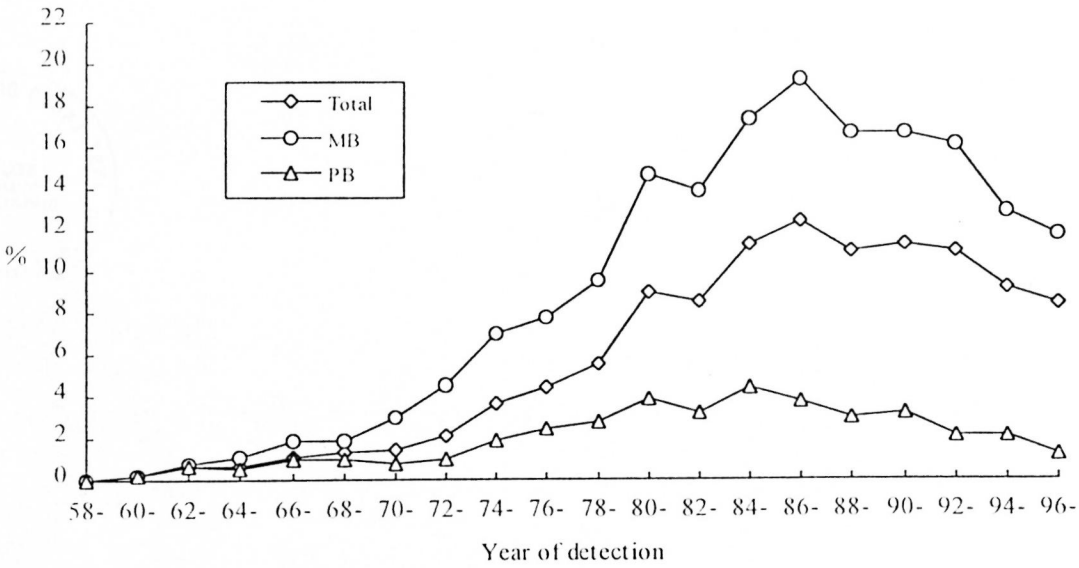

Fig. 1. Cases relapsed after dapsone monotherapy as a proportion of all detected cases, 1958–1997.

well as Taiwan Province and the Hong Kong Special Administrative Region, this system covers 27 provinces, municipalities or autonomous regions (PMRs) in China. The present study on the relapses of leprosy was made in these 27 PMRs.

Patients and follow up. The patients enrolled in the present study were those who had been treated with DDS monotherapy and declared as clinically cured with clinical, bacteriological and histological negativity, and then followed up for more than half a year. For most of these cured patients, the long-term follow up was passive, but at the county and even sub-county levels the network of leprosy control was so powerful that they can almost immediately update the changes (i.e., relapse, death, etc.) in these patients. In addition, a retrospective sifting for the data of all cured, dead and defaulted patients carried out nationide was collected with specialized forms by the local leprosy workers in 1990 and then sent to the National Center for STD and Leprosy Control after having been checked by the prefectural and provincial authorities. For the patients who were clinically cured by DDS before 1990 and still alive after 1990, the deadline for them to be excluded from the cohort of follow up was determined on the basis of the life expectancy of the population. A total of 297,343 leprosy cases cured by DDS monotherapy met the criteria of follow up for the present study and 11,055 relapse patients were used for the analysis.

Criteria of relapses. The diagnosis of relapse after DDS monotherapy was based on the criteria defined in *Practical Lep-*

TABLE 1. *Risk of relapses in 297,343 cases cured with dapsone monotherapy (1960–1995).*

Type of disease	No. cases observed	Average yrs. follow up	No. cases relapsed	Average yrs. incubation	Relaps rate per 100 cases	Relapse rate per 1000 PY[a]
MB	106,518	13.78 ± 8.35	8,675	10.41 ± 6.37	8.14	5.91
PB	190,825	14.47 ± 8.89	2,380	6.43 ± 5.52	1.25	0.86
Total[b]	297,343	14.22 ± 8.71	11,055	9.56 ± 6.41	3.72	2.61
Tests[c]	$t = 20.7$		$t = 12.5$		$\chi^2 = 9083.8$	$\chi^2 = 9371.2$

[a]PY = Patient-years.
[b]Including the cases whose classifications or regimens were unknown.
[c]Student's t and chi-squared tests; $p < 0.001$.

TABLE 2. *Risk of relapses in the first 10 years of follow up of 297,343 cases cured with dapsone monotherapy, 1958–1997.*

Follow up (yrs)	No. cases relapsed			Relapse rate per 100 cases			Rate per 1000 PY[a]			
	MB	PB	Total	MB	PB	Total	MB	PB	Total	p Value[b]
1	279	278	557	10.05	5.44	7.06	106.4	57.43	74.64	<0.001
2	435	350	785	4.95	1.85	2.84	33.47	12.88	19.54	<0.001
3	483	296	779	20.06	6.76	11.48	77.95	26.69	45.06	<0.001
4	528	237	765	20.84	5.44	11.10	58.68	15.39	31.35	<0.001
5	529	201	730	20.14	4.44	10.21	44.07	9.80	22.45	<0.001
6	515	164	679	18.48	3.67	9.36	33.19	6.63	16.86	<0.001
7	526	116	642	16.97	2.43	8.15	25.77	3.71	12.42	<0.001
8	550	117	667	14.53	2.26	7.44	19.18	2.99	9.84	<0.001
9	523	99	622	12.48	1.79	6.39	14.57	2.09	7.46	<0.001
10	484	72	556	10.47	1.16	5.13	10.94	1.21	5.37	<0.001
1–10	4852	1930	6782	12.90	3.04	6.71	25.87	6.87	14.48	<0.001

[a] PY = Patient-years.
[b] Comparison of relapse rates per 1000 patient-years between MB and PB patients (chi-squared test).

rology ([4]), i.e., a "case of relapse" is defined as a clinical and bacteriological reactivation of the disease in a person who has been declared as clinically cured through the strict clinical, bacteriological and pathological evaluations. The criteria were revised in the *Handbook of Leprosy Control* ([8]). The presence of one or more of the following features was considered as evidence for relapse: a) an insidious appearance of new lesions and/or reactivity of lesions that had previously disappeared; b) a reappearance of bacilli (fresh multiplication of surviving leprosy bacilli), i.e., positive reappearance of acid-fast bacilli (AFB) after skin-smear negativity; and c) the specific evidence of relapse and/or positive AFB in the histopathology of a suspected lesion. Operationally, the diagnosis of relapses mainly depends upon bacteriological examination in combination with clinical and histopathological examinations. Relapses after DDS monotherapy can be diagnosed and confirmed by leprosy workers at the district level.

Statistical analysis. The number of patients who relapsed during follow up was used as the numerator and the number of patients who reached clinical cure by DDS monotherapy and their total follow-up duration in terms of patient-years (PY) were used as the denominators for calculation of relapse rates per 100 patients or per 1000 PY. The period in years of follow up was defined as the duration between the calendar year of clinical cure and the year of the patient's exclusion from the cohort of follow up or the end of 1997. The incubation period was made as the duration from the declaration of clinical cure to the diagnosis

TABLE 3. *Risk of relapse in different follow-up periods of 297,343 cases cured with dapsone monotherapy, 1958–1997.*

Follow up (yrs)	No. cases relapsed			Relapse rate per 100 cases			Rate per 1000 PY[a]			
	MB	PB	Total	MB	PB	Total	MB	PB	Total	p Value[b]
1–5	2,254	13,62	3,616	11.78	3.65	6.41	52.64	17.23	29.67	<0.001
6–10	2,598	568	3,166	14.06	2.17	7.09	17.95	2.81	9.13	<0.001
11–15	2,000	268	2,268	8.24	0.75	3.79	6.56	0.60	3.01	<0.001
16–20	1,158	109	1,267	5.76	0.28	2.15	3.31	0.16	1.23	<0.001
21–26	484	52	536	3.78	0.18	1.27	1.69	0.08	0.57	<0.001
26–30	151	15	166	1.82	0.10	0.73	0.67	0.04	0.27	<0.001
31–35	28	6	34	0.98	0.08	0.34	0.31	0.03	0.10	<0.001
36–40	2	0	2	0.34	0.00	0.08	0.09	0.00	0.02	>0.05
	8,675	2,380	11,055	8.14	1.25	3.72	5.91	0.86	2.61	<0.001

[a] PY = Patient-years.
[b] Comparison of relapse rates per 1000 patient-years between MB and PB patients (chi-squared test).

TABLE 4. *Relapse rates in MB patients after treatment with dapsone monotherapy in different large-scale studies (>1000 patients being followed up).*

Study (reference no.)	Country	No. observed patients	Years of follow up	Observed relapse rate[a]
Almeida, *et al.* ([1])	India	1,293	1.9	28.07
Becx-Bleumink ([2])	Ethiopia	1,123	6.6	24.8
Lj ([7])	China	2,234	6–10	7.4
Present study	China	106,518	13.8	5.91[b]

[a] Rate per 1000 patient-years.
[b] Relapse rate during similar period of follow up with the compared studies.

of relapse. For statistical significance, the chi-squared (χ^2) test was used for comparison between the percentages or relapse rates. The mean periods of follow up or the mean incubation of relapses were compared using the Student's *t* test. All statistical tests were done by means of the STATA v.3.0 or Epi-Info 5.0 program. Differences were considered significant at the 95% level of confidence ($p < 0.05$).

RESULTS

Figure 1 shows the proportion of DDS-specific relapses among all detected patients at 2-year intervals between 1958 and 1997. The proportion was less than 2% before the 1970s and gradually increased after the 1970s. For MB patients, the proportion ranged from 13% to 20% of all MB patients during the 1980s and the early 1990s, and decreased from 1986 onward; whereas the proportion in PB patients consistently remained at less than 5% of all PB patients.

Between 1958 and 1997, 297,343 patients (MB 106,518; PB 190,825) had been cured with DDS monotherapy and followed up for an average period of 14.2 ± 8.7 years; 34% had been followed up for 1–10 years, 40% for 11–20 years and another 26% for more than 20 years. All together 11,055 (MB 8675 and PB 2380) relapsed during an accumulated follow-up period of 4,229,050 PY, giving an overall relapse rate of 3.72 per 100 cases or 2.61 per 1000 PY. For either the overall relapse rate per 100 cases or per 1000 PY, the differences between MB (8.14%, 5.91 per 1000 PY) and PB (1.25%, 0.86 per 1000 PY) patients were statistically significant ($\chi^2 = 9083.8$ and 9371.2, respectively, both $p < 0.001$) (Table 1).

Table 2 and Table 3 show the risk of relapse at yearly intervals over the first 10 years and at 5-year intervals of follow up after clinical cure with DDS monotherapy, respectively. The risk of relapse was consistently higher in MB patients than in PB patients in the different periods of follow up, except the period of 36–40 years of follow up. For both MB and PB patients, the relapse rates showed consistently significant decreases year by year ($p < 0.001$, χ^2 test for trend), particularly in PB patients whose relapse rate per 1000 PY was 1.21 in year 10 of follow up; whereas it remained more than 10 per 1000 PY in the MB patients. The relapse rate was higher for the first 10 years for MB (12.9%, 25.87 per 1000 PY) and the first 5 years for PB (3.65%, 17.23

TABLE 5. *Relapse rates in PB patients after treatment with dapsone monotherapy in different large-scale studies (>1000 patients being followed up).*

Study (ref. no.)	Country	No. observed patients	Years of follow up	Relapse rate[a]
Becx-Bleumink ([2])	Ethiopia	1,081	6.6	7.2
Smith and Richardus ([11])	Thailand	1,147	13.9	2.7
Pandian, *et al.* ([9])	India	14,625	<15	5.0
Jesudasan, *et al.* ([5])	India	1,701	3.1	9.71
Li ([7])	China	4,568	1–5	3.9
Present study	China	190,825	14.5	0.86[b]

[a] Rate per 1000 patient-years.
[b] Relapse rate during similar period of follow up with the compared studies.

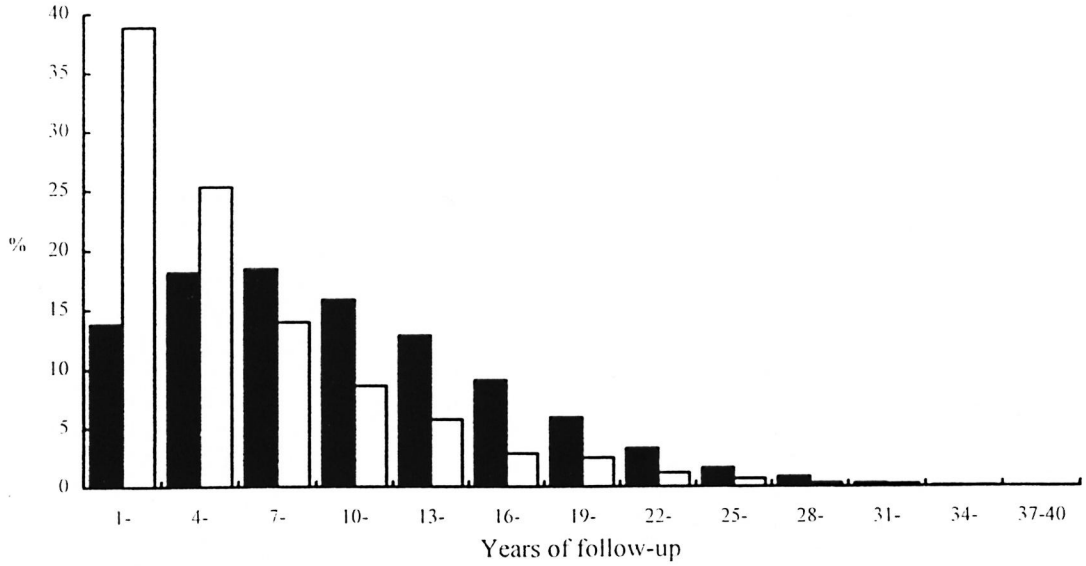

Fig. 2. Relapse in 3-year period as a proportion of all relapses after dapsone monotherapy, 1958–1997. ■ = Multibacillary; □ = paucibacillary.

per 1000 PY) compared with rates during the subsequent years for MB (χ^2 = 1465.6 and 14,165.5, p <0.001) and for PB (χ^2 + 2088.1 and 24,884.5, p <0.001) patients, respectively. Consequently, we considered the follow-up duration as being made up of two distinct periods as to risk of relapse. The relapse rate significantly decreased from 9.51 in the first 20 years to less than 1.7 (1.1 on average) per 1000 PY (p <0.001) after 20 years for MB patients. For PB patients the risk of relapse fell from 6.9 in the first 10 years to less than 0.6 (0.2 on average) per 1000 PY (p <0.001) after 10 years.

Figure 2 gives the percentage of relapse by type (MB, PB) in 3-year incubation periods between clinical cure and diagnosis of relapse for patients cured by DDS monotherapy. It is noted that relapses in PB patients occurred earlier than those in MB patients and, with the extension of follow up, the percentage of relapse decreased significantly (p <0.05) year by year in both MB and PB patients. The percentage either at the first 3 years or during 4–6 years in MB patients (13.8% and 18.1%) was significantly lower than that in PB patients (38.8% and 25.3%) (χ^2 = 754.4 and 60.8, both p <0.01), but relapses among MB patients were more frequent than those among PB patients in the following years. In MB patients more than 60% of relapses occurred after 6 years of follow up; whereas more than 60% of relapses occurred within 6 years in PB patients.

DISCUSSION

Relapse among patients with leprosy after completion of antileprosy treatment is a crucial parameter in assessing the long-term efficacy of chemotherapy. Since the introduction of the sulfones during the 1940s, many studies on relapses have been carried out following discontinuation of treatment. In the present study, the risk of relapses in patients treated with DDS monotherapy was analyzed for the purpose of enhancing our correct understanding of this problem. In addition, although there are very few patients treated with DDS monotherapy at present, it is still important to evaluate the relapses in the patients treated with this regimen, from which we can not only provide the scientific basis for the management of DDS-cured patients, but can obtain some enlightenment and accumulate some experience for the present implementation of MDT, because we have, at best, only about 10 years' experience in MDT implementation.

The main feature of this study, compared with most published studies ([10–12]), is that the data came from a large project consisting of a large number of patients for ob-

serving the relapses within a whole country, which covers an area of 9.6 million square kilometers and had an estimated population of 1.2 billion in 1996.

At the beginning of the organized control of leprosy in the mid-1950s and along with the consequent efforts in case finding through the comprehensive measures, the number of newly detected cases increased markedly, forming a peak detection rate of 5 per 100,000 in 1958–1959. But the relapsed patients were very few, accounting for less than 1% of all patients detected annually (Fig. 1), mainly because of the limited number of cases who were declared as clinically cured at that time. However, with the further implementation of the leprosy control program and the gradual decrease in the number of newly detected cases, the proportion of relapses among the active cases detected increased steadily in the 1970s and then remained at 13%–20% for all detected MB cases between the 1980s and the early 1990s; the proportion of relapses among newly detected PB cases consistently remained at 2%–5% (Fig. 1). The main reason for the increase in the proportion of relapses among newly detected active cases in the 1980s was most probably that, through intensified case finding for MDT implementation, some backlog of relapsed cases released from DDS treatment were detected. However, the proportion of relapses decreased from 1986 onward due to the timely detection of them after MDT introduction and to very little backlog of relapsed cases.

In the past decades, many well-documented studies have been reported. Although the various studies are difficult to interpret because of much variation in the dosages and durations of treatment, the period and methods of follow up and the criteria for the diagnosis of relapses, we present the results of the studies with more than 1000 MB and PB patients in Table 4 and Table 5, respectively.

As has been shown in many studies ([2, 9, 11]), the overall relapse rate and the rates in the different periods were significantly higher in MB patients than in PB patients in the present study ($p < 0.05$). An overall relapse rate of 0.86 per 1000 PY over an average period of 14.5 years in PB patients and 5.91 per 1000 PY over an average period of 13.8 years in MB patients in the present study were significantly lower than the studies presented in Table 4 and Table 5. Moreover, the rates were not comparable with the studies by Kurz, *et al.* ([6]), Cartel, *et al.* ([3]) and Smith and Richardus ([11]) in MB patients and Smith and Richardus ([11]) in PB patients, which showed that some patients also continued dapsone during the follow-up period. The difference with the above-mentioned studies was most likely due to the fact that the mean duration (14.2 ± 8.7) of follow up in the present study was not only longer than the above-mentioned studies, but also larger than the mean incubation period of the observed DDS relapses, suggesting that only a few relapses are expected to occur as the follow up is prolonged. In addition to this, two other explanations for the difference may be that a) many patients in the present study were still kept on a maintenance treatment with DDS (50–100 mg daily for as long as 5 years for PB and 10 years or life-long for MB patients) after reaching clinical cure, with the result that some patients were still on DDS treatment during their follow up, and b) the great majority of patients in the present study were treated as inpatients in leprosy hospitals or villages with a very high regularity of treatment. However, the first explanation was not supported by the findings in the comparable studies ([3, 6, 11]) in which patients also continued dapsone during their follow up. The relapse rates were significantly decreased with the duration periods of follow up in both MB patients and PB patients. The findings of decreases in the relapse rates from 9.51 at the first 20 years to less than 1.7 per 1000 PY after 20 years in MB patients and from 6.9 at the first 10 years to less than 0.6 per 1000 PY after 10 years in PB patients imply that the risk of relapse after patients are released from dapsone monotherapy will decrease to a very low level when the patients are observed for more than 20 years in MB or 10 years in PB leprosy.

CONCLUSION

From the findings of the present study, it can be concluded that the overall relapse rates in MB and PB patients cured by DDS

monotherapy were acceptably low, and most of these patients have been followed up for more than a mean incubation period of observed dapsone relapses. Therefore, along with the further extension of follow up the risk of relapses in dapsone-cured patients will not be expected to increase but will gradually decrease, although the relapses after DDS monotherapy will still account for a significant proportion of the total relapsed cases for a period of time. It is necessary to be concerned with this when planning policies for the management of patients released from dapsone monotherapy. In addition, the re-occurrence of the disease in some patients may be attributed to re-infection rather than relapse of the original infection.

SUMMARY

Based upon the data from the Chinese National System for Leprosy Surveillance, this paper reports on the relapses in 297,343 leprosy patients [multibacillary (MB) 106,518, paucibacillary (PB) 190,825] cured by dapsone monotherapy. A total of 11,055 (MB 8675, PB 2380) patients relapsed during an accumulated follow-up period of 4,229,050 patient-years (PY), giving an overall relapse rate of 3.72 per 100 cases or 2.61 per 1000 PY, i.e., 8.14% or 5.91 per 1000 PY over an average follow-up period of 13.8 ± 8.4 years in MB patients and 1.25% or 0.86 per 1000 PY over an average period of 14.5 ± 8.9 years in PB patients. For either the overall relapse rate per 100 cases or per 1000 PY, the differences between MB and PB patients were statistically significant, except during 36–40 years of follow up. For both MB and PB patients, the relapse rates showed consistently significant decreases year by year, particularly in PB patients whose relapse rate per 1000 PY was 1.21 in year 10 of follow up; whereas it remained more than 10 per 1000 PY in MB patients. In view of that, the overall relapse rates in MB and PB patients cured by dapsone monotherapy were acceptably low, and most of these patients have been followed up for more than a mean incubation period of observed dapsone relapse. Along with the further extension of follow up, the risk of relapse in dapsone-cured patients will not be expected to increase. This conclusion should be considered when planning policy for the management of patients released from dapsone monotherapy.

RESUMEN

Con base en los datos del Sistema Nacional Chino para la Vigilancia de la Lepra, en este articulo se reportan las recaidas en 297,343 pacientes con lepra (106, 518 mutibacilares, MB, y 190, 825 paucibacilares, PB), curados con monoterapia con dapsona. Un total de 11, 055 pacientes (8675 MB y 2380 PB) recayeron durante un periodo de seguimiento acumulado de 4,229,050 paciente años (PA), dando una tasa de recaida global de 3.72 por 100 casos ó 2.61 por 1000 PA, i.e., 8.14% ó 5.91 por 1000 PA, en un periodo de seguimiento promedio de 13.8 ± 8.4 años en los pacientes MB, y 1.25% ó 0.86 por 1000 PA en un periodo de seguimiento promedio de 14.5 ± 8.9 años en los pacientes PB. Las tasas globales de recaida por 100 casos ó por 1000 PA fueron estadisticamente diferentes entre los pacientes MB y PB, excepto para el periodo de 36–40 años de seguimiento. Tanto para los pacientes MB como para los PB, las tasas de recaída mostraron decrementos consistentemente significantes año tras año, particularmente en los pacientes PB, cuya tasa de recaída por 1000 PA fue de 1.21 en el año 10 del seguimiento, mientras que ésta permaneció mayor de 10 por 1000 PA en los pacientes MB. La tasa global de recaída en los pacientes MB y PB curados con monoterapia con dapsona ha sido aceptablemente baja; la mayoria de los pacientes han estado vigilados durante un periodo mayor al tiempo de incubación promedio de las recaídas observadas en los pacientes tratados con dapsona. No obstante la extensión del tiempo de seguimiento, no se espera que el riesgo de recaída aumente en los pacientes curados con dapsona. Esta conclusion debe ser considerada cuando se planeen las estrategias para el manejo de los pacientes tratados con monoterapia con dapsona.

RÉSUMÉ

Cet article, basé sur les données provenant du Système National Chinois de Surveillance de la Lèpre, décrit les rechutes chez 297 343 patients atteints de lèpre [106 518 multibacillaire (MB), 190 825 paucibacillaire (PB)] et soignés par monothérapie à la dapsone. Un total de 11 055 (8675 MB et 2380 PB) ont rechuté durant une période cumulée de 4 229 050 personnes-par-année (PPA), donant un taux de rechute global de 3,72 cas pour 100 patients (3,72%) ou 2,61 pour 1000 PPA et, plus précisément, 8,14% ou 5,91 pour 1000 PPA sur une période de suivi de 13,8 ± 8.4 années chez les patients MB et 1,25% ou 0,86 pour 10 000 PPA sur une période de suivi de 14,5 ± 8.9 années chez les patients PB. Que ce soit le taux global pour 100 cas ou celui pour 1000 PPA, les différences entre patients MB et PB étaient statistiquement significatives, à l'exception des cas ayant 36–40 années de suivi. Les taux de rechute pour les patients à la fois MB et PB montrèrent une diminution d'incidence au cours du temps, en particulier chez les patients PB

dont le taux de rechute pour 1000 PPA était de 1,21 à 10 ans de suivi; tandis qu'il est resté à plus de 10 pour 1000 PPA pour les patients MB. Au vu de ces résultats, la proportion globale de rechute chez les patients MB et PB traités par monothérapie est restée à des taux bas acceptables, et la plupart des patients ont été suivi sur une période supérieure à celle de la période moyenne d'incubation des rechutes après traitement par la dapsone. Concomitant avec l'extension de la période de suivi, le risque de rechute chez les patients ne devrait pas augmenter. Cette conclusion devrait être prise en considération lorsque des décisions sur les mesures à prendre pour gérer les patients après monothérapie à la dapsone.

Acknowledgment. This work was financially supported and efficiently coordinated by the Ministry of Health of China. We gratefully acknowledge the staff of the institutions of dermatology at provincial, municipal, district and county levels for their help in obtaining the data used in the study. We also wish to thank all of the other people who made any contribution to the preparation of this paper.

REFERENCES

1. ALMEIDA, J. G., CHRISTIAN, M. and CHACKO, C. J. Follow up of lepromatous (LL and BL) patients on dapsone (DDS) monotherapy after attainment of smear negativity in Gudiyatham Taluk, South India. Int. J. Lepr. **51** (1983) 382–384.
2. BECX-BLEUMINK, M. Relapse in leprosy patients after release from treatment from dapsone monotherapy; experiences in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia. Int. J. Lepr. **60** (1992) 161–172.
3. CARTEL, J.-L., BOUTIN, J.-P., SPIEGAL, A., PLICHART, R. and ROUX, J.-F. Longitudinal study on relapses of leprosy in Polynesian multibacillary patients on dapsone monotherapy between 1946 and 1970. Lepr. Rev. **62** (1991) 186–192.
4. EDITORIAL GROUP. *Practical Leprosy.* Nanjing: Jiangsu People's Publishing House, 1976, pp. 333–335.
5. JESUDASAN, K., CHRISTIAN, M. and BRADLEY, D. Relapse rates among nonlepromatous patients released from control. Int. J. Lepr. **52** (1984) 304–310.
6. KURZ, X. M., DECLERQ, E. E. and VELLUT, C. M. Rate and time distribution of relapses in multibacillary leprosy. Int. J. Lepr. **57** (1989) 599–606.
7. LI, H. Y. Problems of leprosy relapse in China. Int. J. Lepr. **61** (1993) 1–7.
8. MA, H. D. *Handbook of Leprosy Control.* Nanjing: Jiangsu Science and Technology Press, 1989, pp. 269–270.
9. PANDIAN, T. D., MULIYIL, J. and VELLUT, C. Risk of relapse among nonlepromatous patients released from treatment after dapsone monotherapy. Lepr. Rev. **61** (1991) 288–296.
10. PEAT, M., BROLIN, L., GANAPATI, R., MCDOUGALL, A. C., REVANKAR, C. R. and WATSON, J. W. An evaluation of the contribution of the Swedish International Development Authority (SIDA) to leprosy control in India based on the implementation of multiple drug therapy (MDT) 1981–1993. Indian J. Lepr. **67** (1995) 447–465.
11. SMITH, T. C. and RICHARDUS, J. H. Relapse rates in patients treated with dapsone monotherapy and combinations of dapsone and thiambutosine, thiacetazone, isoniazid and streptomycin in the pre-MDT era. Int. J. Lepr. **62** (1994) 353–358.
12. WORLD HEALTH ORGANIZATION. Chemotherapy of leprosy. Geneva: World Health Organization, 1994. Tech. Rep. Ser. 847.