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Epidemiology of leprosy and response to treatment in Hong Kong

痲瘋在香港的流行病學和治療效果

Objectives. To review the reported trend of leprosy in Hong Kong.
Design. Retrospective study.
Setting. Three major leprosy clinics in Hong Kong.
Patients. Leprosy patients registered between 1970 and 2004.
Main outcome measures. Incidence, rate of deformities, distribution of leprosy subtypes, age distribution, and relapses after therapy.
Results. The incidence of leprosy has decreased from 3.2 per 100 000 population in 1970 to 0.088 per 100 000 population in 2004. The proportion of the three subtypes of leprosy has remained roughly equal. There have been 87 relapses within this period with 54 (62%) cases of lepromatous leprosy, 22 (25%) borderline leprosy, and 11 (13%) tuberculoid leprosy. The overall relapse rate was 6.7% (0.2 per 100 person-years); this can be subdivided as a relapse rate for multidrug therapy of 3.2% (0.33 per 100 person-years) and for dapsone monotherapy of 8.3% (0.2 per 100 person-years). The mean interval to relapse for multidrug therapy and dapsone monotherapy was 1.83 and 5.8 years, respectively. The mean duration till relapse for patients on dapsone monotherapy was 15.6 years.
Conclusion. Treatment with recommended WHO-multidrug therapy is effective and well tolerated. Dapsone monotherapy is no longer effective. Leprosy is well controlled in Hong Kong but continued surveillance is required to detect relapses and to ensure good patient compliance with treatment.

目的：按香港痲瘋趨勢的報告作出檢討。
設計：回顧性研究。
安排：香港三間主要痲瘋診所。
患者：1970 至 2004 年間，在上述的痲瘋診所登記的病人。
主要結果測量：發病率、身體畸形情況、痲瘋支類分佈、年齡分佈和治療後復發的情況。
結果：痲瘋的發病率，由 1970 年每 100 000 人口有 3.2 人，下跌至 2004 年每 100 000 人口只有 0.088 人，而三種痲瘋病支類的分佈歷年相等。痲瘋復發的病人有 87 人，其中 54 人（佔 62%）屬於結節性痲瘋，22 人（佔 25%）屬於邊界型痲瘋，而 11 人（佔 13%）屬於結核節狀型痲瘋。病人整體復發率為 6.7%（每 100 人年有 0.2 人），其中接受多種藥物治療的病人復發率為 3.2%（每 100 人年有 0.33 人），而只用氨苯藥物治療的病人復發率為 8.3%（每 100 人年有 0.2 人）。而復發的平均週期，接受多種藥物治療的病人為 1.83 年，只用氨苯藥物治療的病人則為 5.8 年。只用氨苯藥物而復發的病人，復發時平均已用藥 15.6 年。
結論：世界衛生組織建議的多種藥物治療法有效且持久，單以氨苯治療已不再有效。痲瘋在香港得到有效控制，但仍須要持續監察，並確保病人依指示接受治療。

Key words:
Dapsone;
Drug therapy;
Leprosy;
Recurrence

關鍵詞：
氨苯；
藥物治療；
痲瘋；
復發

Hong Kong Med J 2006;12:174-9

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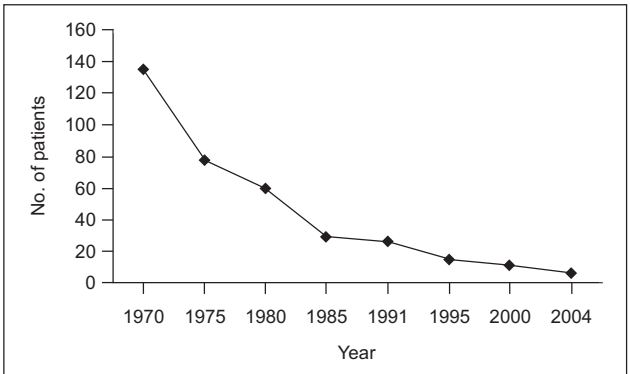
Introduction

There has been a steady decline worldwide in the incidence of leprosy, especially after the introduction of multidrug therapy by the World Health Organization (WHO-MDT) in 1982.[1] There have nonetheless been reports of relapse, albeit at a low rate, after stopping WHO-MDT. In 1991, the WHO set a target for eliminating leprosy as a public health problem (defined as <1 case per 10 000 population) by the year 2000. On a global basis, the number of registered cases fell from 5.4 million in 1985 to 0.88 million in 1997 and by the end of 1993, 5.6 million patients had been cured.[1] There has been a steady decline in the



Year	No. of new cases	Incidence rate per 100 000 population	Incidence rate per 100 000 person-years
1970	135	3.2	359.9
1975	78	1.7	218.4
1980	60	1.1	160
1985	29	0.5	77
1991	26	0.4	69
1995	15	0.24	40
2000	11	0.16	29
2004	6	0.088	16

Fig. Incidence of leprosy, 1970-2004

incidence of leprosy in Hong Kong, following improved living conditions and the introduction of WHO-MDT in 1982. The current study aimed to investigate leprosy trends in Hong Kong between 1970 and 2004.

Methods

Case records of leprosy patients registered between 1970 and 2004 at Social Hygiene Service leprosy clinics in Hong Kong were analysed. The Social Hygiene Service is part of the Centre for Health Protection (CHP), and is responsible for the care of leprosy patients in the public sector. Diagnosis of leprosy is based on clinical presentation, skin biopsy, and skin smear. New cases are examined for deformities by the attending physician. Confirmed cases of leprosy are reported to the CHP for statistical purposes.

Treatment of leprosy in Hong Kong is based on the WHO-MDT regimen. For negative skin-smear cases, paucibacillary multidrug therapy consisting of dapsone 100 mg/day (unsupervised) and rifampicin 600 mg/month (supervised) is prescribed for at least 1 year. For positive skin-smear cases, multibacillary multidrug therapy (MB-MDT) consisting of dapsone 100 mg/day (unsupervised), clofazimine 50 mg/day (unsupervised), rifampicin 600 mg/month (supervised), and clofazimine 300 mg/month (supervised) are prescribed for at least 2 years or until negative smear, whichever is longer.

The characteristics studied included country of origin (country of birth), coverage (proportion of confirmed leprosy cases under treatment), incidence of WHO grade 2 deformities (visible deformities due to leprosy), age distribution, distribution of the different types of leprosy, bacterial index (BI), morphological index (MI) meaning the % of live bacilli in smears, incidence of lepra reactions, and relapses after dapsone monotherapy (DDS) and WHO-MDT.

Table 1. Origin of leprosy patients, 1970-2004

Country of origin	Total No. of patients	Relapsed patients No. (%)
China	1303	79 (90.8)
Burma	2	1 (1.2)
The Philippines	55	1 (1.2)
Hong Kong	94	3 (3.4)
Indonesia	28	2 (2.2)
Holland	1	1 (1.2)
Nepal	40	0
Venezuela	1	0
India	18	0
United States	1	0
Vietnam	31	0

Annual reports of the incidence and prevalence of leprosy were reviewed. Paediatric cases referred to children under 16 years of age at the time of diagnosis. The relapse rate was calculated by dividing the number of relapses by the number of patients at risk of relapse. The denominator was calculated by subtracting the number of patients who had died and who had defaulted from the total number of patients registered during this period. Relapse was defined as a positive BI on two consecutive smears or by clinical relapse.[2] Time to relapse was defined as the duration between stopping treatment and time of relapse. Between-group comparisons were made by Student's *t* test.

Results

Epidemiology

A total of 1574 patients were registered between 1970 and 2004. There were 163 deaths and 114 patients defaulted from follow-up. The actual number of patients under review was 1297. The decreasing incidence of leprosy is shown in the Figure.

Between 1970 and 1979, 90% (847) of new cases originated from China. This proportion decreased to 86% (373) between 1980 and 1990, and to 46.7% (63) from 1991 to 2000. Between 2001 and 2004, 69% (20) of new cases were from China. The remaining cases were from South-East Asia (the Philippines, Nepal, Vietnam, Indonesia, Burma) [Table 1]. Between 1970 and 1999, 93 new cases originated from Hong Kong: over 50% of these patients had lived in Hong Kong for 11 years or more. The prevalence had decreased from 0.25/10 000 population in 1984 to 0.18/10 000 population in 1990 and to 0.053/10 000 population in 2004. The mean age of new patients increased during this period (Table 2). The majority of patients between 1975 and 2004 were between 21 and 50 years of age. Paediatric cases are now rare, with only two cases documented in Hong Kong since 1980. Both were male (9 and 11 years old).

Table 2. Change in age distribution of leprosy patients

Age-group (years)	Year				
	1965	1975	1984	1995	2004
0-10	5 (3%)	0	0	1 (7%)	0
11-20	21 (13%)	6 (8%)	1 (3%)	0	0
21-30	47 (29%)	17 (22%)	9 (28%)	2 (13%)	2 (33%)
31-40	37 (23%)	18 (23%)	7 (22%)	2 (13%)	0
41-50	25 (15%)	11 (14%)	1 (3%)	3 (20%)	1 (17%)
51-60	16 (10%)	17 (22%)	2 (6%)	5 (33%)	1 (17%)
>60	13 (8%)	10 (13%)	12 (38%)	2 (13%)	2 (33%)
Total	164	79	32	15	6

Between 1970 and 1999, 45% of cases were tuberculoid leprosy (TT), 25% were borderline leprosy (BB), and 30% were lepromatous leprosy (LL). From 1995 to 2004, 24% of new cases were TT, 42% were BB, and 34% were LL. A total of 45 patients with active leprosy were detected on contact tracing (28 active TT, 10 BB, and 7 LL) between 1970 and 2004. The mean age of these cases was 27.9 years.

Compliance with MDT has generally been good. Coverage within this period varied between 75% and 100%. The relatively high proportion of new cases from South-East Asia and the repatriation of Vietnamese refugees contributed to the number of defaulted follow-ups.

There was a decline in the incidence of deformities. Between 1970 and 1999, the proportion of leprosy cases with WHO grade 2 deformities (claw hand, foot-drop, eye deformities) was 22%, with peripheral neuropathy 12.4%, and with evidence of nerve thickening 28.1%. The mean incidence of WHO grade 2 deformities in new cases decreased to 10% between 2000 and 2004.

Response to therapy

Dapsone monotherapy was prescribed to 780 patients between 1970 and 1982 and MDT to 697 between 1982 and 2004. In the former patients, 57 (7.3%) developed type 1 reactions (a reversal reaction caused by changes in cell-mediated immunity; clinically, new lesions may appear and there is swelling and tenderness of existing lesions, and nerve damage may occur in untreated cases) and 51 (6.5%) manifested type 2 reactions (an immune complex condition presented with recurrent crops of red, tender nodules with or without pyrexia; the eyes, nerves, testes, joints, kidneys, and lymph nodes may also be affected). In those treated with MDT, 55 (7.9%) were type 1 reactions and 43 (6.2%) were type 2. The overall incidence of reactions on DDS was 13.8% and on MDT 14.1%. The overall (DDS and MDT) incidence of lepra reactions was 14% while the overall duration of type 1 reactions varied from 1 to 19 months and type 2 reactions from 1 to 12 months.

Type 1 reactions occurred mainly in the BB and LL types of leprosy while type 2 reactions mainly affected LL and borderline lepromatous (BL) cases. Of the cases which had type 1 and type 2 reactions, the proportion that occurred during the first year of treatment was 84% and 75%, respectively. Systemic steroids were effective for all cases of type 1 reactions and 40 (93%) of 43 cases of type 2 reactions. Thalidomide was required to treat a type 2 reaction in three cases. Thalidomide caused mild dizziness in one patient at a dose of 100 mg/day but was otherwise tolerated. Late reactions (type 1 and type 2) were seen in three cases and retreated with MDT and systemic steroids.

In patients treated with MDT, 12 (1.7%) developed haemolytic anaemia, seven (1.0%) demonstrated deranged liver function due to dapsone, and three (0.4%) had skin eruptions due to dapsone. Dapsone was replaced by minocycline, clarithromycin, or ofloxacin in these patients and had comparable efficacy. One (0.1%) patient prescribed dapsone developed thrombocytopenia but recovered when treatment was stopped. Rifampicin was well tolerated; one patient had thrombocytopenia that resolved on stopping the drug. Minocycline was substituted with equal efficacy, although this was complicated by slate-grey pigmentation of the shins.

Relapse after dapsone monotherapy

Between 1970 and 2004, there were a total (DDS and post-MDT) of 87 relapses—54 (62%) LL, 22 (25%) BB, and 11 (13%) TT. There was a relapse of leprosy in 31 (47.7%) patients after DDS was stopped (relapse rate 0.08/100 person-years) and in 45 (69.2%) during DDS (relapse rate: 0.12/100 person-years). The relapse rate for DDS was 8.3% (0.20 per 100 person-years). There was a male predominance in LL cases with a male to female ratio of 2.9:1.

Relapse in 25 patients prescribed DDS occurred between 1970 and 1976, 11 between 1977 and 1991, and 30 between 1992 and 1999. Patients relapsed a mean of 5.8 years (range, 11 months-12 years; median, 5 years) after stopping dapsone and had been treated with dapsone for a mean of 30.5 years (range, 8-42 years; median, 26 years). Patients who relapsed during DDS had been taking dapsone for a mean of 15.6 years (range, 5-46 years; median, 12 years).

Of the 87 relapsed cases, 24 (27.6%) had a BI of more than 3 on initial presentation. In patients treated with DDS, there was a significant difference between the initial mean BI of 2.0 (range, 0.30-13.8; median, 3) and mean BI of 1.07 (range, 0.16-4; median, 0.6) on relapse (P=0.012). The mean MI was 10% (range, 0-60%; median, 5%) on diagnosis and 0.12% (range, 0-2.0%; median, 0%) on relapse. Thirteen cases were smear-negative on presentation but became smear-positive on relapse.

Seventy-nine (90%) of all patients who relapsed originated from China (Table 1). Five of these patients became smear-positive while on dapsone during the 1970s—three of them had taken dapsone for 20 years, of whom two received an addition of clofazimine before achieving

Table 3. Relapses after multidrug therapy, 1970 to 2004

Patient No.	Type* (initial)	Sex/age (years)	Treatment†	Time to relapse	Bacterial index (initial)	Bacterial index (relapse)	Type* (relapse)
1	TT	F/53	PB-MDT	1 year	Negative	Negative	TT
2	TT	F/28	PB-MDT	2 years	Negative	Negative	TT
3	TT	M/30	PB-MDT	2 years	Negative	Negative	BB
			MB-MDT				
4	LL	M/70	DDS	1.35 years	4.8	0.5	LL
			MB-MDT	2.2 years		Negative	TT
5	BB	M/46	MB-MDT	5 years	1.83	0.16	BB
6	BB	M/38	MB-MDT	3 years	2.3	Negative	LL
7	LL	F/45	DDS	4 years	2.5	2.6	LL
			MB-MDT			Negative	LL
8	TT	M/42	DDS	1 year	Negative	1.6	LL
			MB-MDT			0.33	LL
9	LL	M/56	MB-MDT	3 years	3	Negative	LL
10	LL	F/24	MB-MDT	2 years	3.5	Negative	LL
11	LL	M/32	MB-MDT	16 years	1.0	Negative	LL
12	BT	M/47	MB-MDT	2 years	Negative	Negative	BT
13	BL	M/34	MB-MDT	8 years	3.0	Negative	LL
14	LL	M/68	MB-MDT	1 year	0.3	Negative	LL
15	BT	M/60	MB-MDT	8 months	0.6	Negative	BT
16	BB	F/29	MB-MDT	2 years	Negative	Negative	LL
17	BL	F/44	MB-MDT	10 years	0.5	Negative	BL
18	LL	M/47	MB-MDT	1 year	Negative	Negative	LL
19	LL	M/47	MB-MDT	3 years	2.6	Negative	LL
20	LL	M/15	DDS	3 months	4.5	Negative	LL
			MB-MDT			Negative	LL
21	TT	F/26	MB-MDT	10 months	Negative	Negative	BL
22	LL	F/25	MB-MDT	9 months	1	Negative	LL

* TT denotes tuberculoid leprosy, LL lepromatous leprosy, BB borderline leprosy, BT borderline tuberculoid leprosy, and BL borderline lepromatous leprosy
† PB-MDT denotes paucibacillary multidrug therapy, MB-MDT multibacillary multidrug therapy, and DDS dapsone monotherapy

smear negativity. In the remaining patients, leprosy was controlled by increasing the dose of dapsone. Smear negativity after increasing dosage or adding clofazimine occurred after a mean of 4 years (range, 1-9 years; median, 3.5 years). Patients who relapsed on DDS were switched to MDT once it was introduced and all patients had resolution of lesions (smear-negative) in a mean of 1 year.

Relapse after multidrug therapy

Since the introduction of MDT in 1982, 697 cases have been treated. There have been 22 relapses after MDT between 1970 and 2004. The relapse rate for MDT was therefore 3.2% (0.33 per 100 person-years) and the overall relapse rate was 6.7% (0.23 per 100 person-years).

The mean time to smear negativity of patients with MDT was 1.76 years (range, 1-4 years; median, 2 years), compared with 3.9 years of those with DDS. Characteristics of patients with MDT are shown in Table 3. Of the relapses, 10 (45%) were LL, seven (32%) BB (including borderline tuberculoid leprosy [BT] and BL), and five (23%) TT. There was a significant difference between the mean initial BI (1.37) and mean BI on relapse (0.16; P=0.002). There was also a significant difference in the mean BI of relapsed patients treated with MDT and those treated with DDS (P=0.014). The mean time to relapse was 1.83 years (range, 3 months-16 years; median, 2 years) after MDT; 8 (3TT, 4LL, 1BT) of the 22 patients relapsed within 1 year.

There was no record of previous dapsone therapy except in three patients and all cases relapsing after MB-MDT had been on dapsone maintenance therapy.

Discussion

The reported incidence of leprosy in Hong Kong in the public sector has decreased over the past 30 years, from 135 cases per year in 1970 to six cases in 2004.[3] In addition, the mean age of new cases has increased, with fewer children being affected. In 1965, five patients were aged below 10 years and 21 were between 11 and 20 years.[4] Paediatric cases are now rarely seen. The incidence of deformities is also lower as a result of improved treatment and health care. Coverage by MDT has remained high, largely due to the fear and stigma still associated with leprosy.

Statistically, BB and LL types have become more common in the past 10 years. Nonetheless with the decreased actual number of new cases, the number of BB and LL cases remains low. Approximately 30 to 40% of leprosy cases in oriental patients from China, Korea, and Japan are LL. In contrast, 90% of cases in Africa are TT.[5] This reflects the influence of racial/genetic differences on the prevalence of the two types of leprosy.

Findings from the current study show that MDT is effective and well tolerated. In patients who could not tolerate standard MDT, ofloxacin, clarithromycin, and minocycline have been proven to be suitable alternatives with confirmed efficacy.[6,7]

There are various limitations to this study. The relapse rate for DDS may have been underestimated as relapses in the field due to death or default would not have been detected. In addition, patients being cared for by the private sector were not studied. Nonetheless since leprosy is a notifiable disease, underreporting would have been minimal. Incidence rates were calculated from reported cases of leprosy and did not include undetected cases in the community. Despite these limitations, this study revealed a definite decreasing trend in the incidence of leprosy over the past 30 years.

Dapsone resistance developed during the period of DDS is the likely cause in patients who relapse during or after treatment.[1] The exact prevalence of dapsone resistance in Hong Kong is unknown but is increasingly common worldwide. In the Philippines, it has increased from 3.6% in 1975 to 52.7% in the period 1988-1992.[8] Similarly, primary dapsone resistance in China was reported to be 44% in 1989.[9] Similar figures may apply to dapsone resistance in Hong Kong and as such DDS should no longer be prescribed. As reported elsewhere, international travel and immigration to and from leprosy-endemic countries will continue to influence the disease pattern.[10]

There was a higher proportion of relapses between 1970 and 1976 (25 patients) that coincided with the period of dapsone resistance. The introduction of MDT may have led to fewer relapses between 1977 and 1990 (11 patients). Subsequently, between 1992 and 1994, treatment was stopped in patients who had completed a mean of 35.6 years of DDS: this coincided with the increased incidence of relapses between 1992 and 1999 (30 patients).

The majority of post-MDT relapses were of the BB or LL type, and the male to female ratio was 1.75:1. Nonetheless the initial BI was not particularly high: only two patients had a BI of more than 4 and both were of LL type. *Mycobacterium leprae* can be found in the lymph nodes and nerves in some slit skin smear-negative cases after WHO-MDT, especially in those with a BI of more than 4.[11] Surveillance after treatment is therefore important.

There was a significant difference between the mean BI at diagnosis and at relapse in patients on DDS, indicating that DDS effectively suppressed the disease. The decrease in BI with MDT was nevertheless significantly greater than that with DDS, suggesting that MDT is more effective. The lower BI at relapse suggests that persister *M leprae* are responsible for relapses.

Reported WHO-MDT relapse rates vary between less than 1% and 17.7%.[12-16] The relapse rate after MDT of 3% (0.30/100 person-years) in this study is comparable but would be expected to increase with a longer follow-up period. Jamet and Ji[13,17] reported a relapse rate of 2.9% in multibacillary patients at 2 years that increased to 20% at a mean follow-up period of 72.7 (standard deviation, 17.3) months. Fifty percent of multibacillary relapses occurred in the first year and 50% of paucibacillary relapses occurred within 2.5 years. This is comparable with the findings of the current study. The reported relapse rates after discontinuation of DDS vary from less than 1% to 17% for TT[18,19] and from 2% to 30% for LL.[18,20] This is again comparable with the findings in this study. The relapse rate for MDT was lower than that for DDS (3.2% vs 8.3%) although the mean time to relapse for the MDT cases was shorter (1.83 years vs 5.8 years). These patients were also taking dapsone maintenance therapy after MDT and probably constituted a subgroup that was likely to relapse due to dapsone resistance.

In this study, the incidence of lepra reactions on DDS was lower but similar to that seen with MDT (14%). The addition of clofazimine may reduce the frequency of type 2 reactions but not type 1 reactions. Systemic steroids were effective in these patients and were important in preserving nerve function. The overall reported incidence of lepra reactions during MDT has varied from 22.8% to 45% with an incidence of type 1 and type 2 reactions of 8.09% and 4.7%, respectively.[21-23] Another study reported the highest incidence of reactions in the first year of MDT and in the 6 months after MDT, with reactions occurring up to 7 years after MDT.[24] Continued surveillance is required.

Conclusion

The current study shows that the reported incidence of leprosy in Hong Kong has decreased and MDT is effective and well tolerated. Due to the emergence of dapsone resistance, DDS is no longer appropriate for treatment. There have been cases of relapse after MDT, indicating the problem of persister *M leprae*, highlighting the need for continued surveillance, especially as MDT relapses may occur late.

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