

Long-term efficacy of single-dose mass treatment with diethylcarbamazine citrate against diurnally subperiodic *Wuchereria bancrofti*: eight years' experience in Samoa

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A single-dose of diethylcarbamazine citrate (DEC, 6 mg per kg body weight) was administered in three mass treatment campaigns to >80% of the estimated total Samoan population (160 000) in 1982, 1983, and 1986. The effect of the drug was evaluated before and after each campaign by conducting four blood surveys covering 9600 to 13 700 people from 26–34 villages on each occasion. The drug reduced the prevalence of Wuchereria bancrofti microfilariae from 5.6% to 2.5% (a 55% reduction), while the transmission potential (the estimated mosquito infection rate if everyone is equally exposed to mosquito bites) dropped from 2.18 to 0.67 (a 70% reduction). The total number of microfilariae in the Samoan population is estimated to have been reduced by 80%. A spaced, single-dose treatment with DEC at a 1–2-year interval therefore seems to be an effective control measure against diurnally subperiodic W. bancrofti.

Introduction

Diethylcarbamazine has been the most effective, safe and widely used antifilarial drug since Hewitt et al. first reported its efficacy in 1947 (1). Subsequently, various dosage schedules suitable for the treatment of different species and types of filarial parasites have been compared (2). In 1974, the importance of

administering an adequate total dose (72 mg per kg body weight) of diethylcarbamazine citrate (DEC) for *Wuchereria bancrofti* infection was stressed by a WHO Expert Committee (3). Since then a 12-dose treatment (6 mg per kg) has been used worldwide as a standard regimen. However, use of this regimen poses considerable difficulties in large-scale mass treatment campaigns when the administrative backup is reduced or the enthusiasm of local people wanes. In several countries DEC-medicated cooking salt has been used to facilitate mass treatment and has proved to be very effective and safe (4–7). In the South Pacific, annual single-dose treatments with DEC (6 mg/kg) are effective in decreasing the prevalence of microfilariae (mf), and the treatment schedule is operationally straightforward (8–10). However, the long-term effect of this reduced dosage treatment has not yet been assessed critically. Meanwhile, ivermectin, the drug of choice for treating onchocerciasis (11–13), has been tested on lymphatic-dwelling filariae with promising results. A single dose of ivermectin has been reported to be as effective as a full course of treatment with DEC (14). Whether ivermectin can replace DEC is arguable, but it is essential to study the effect of a single dose of DEC rather than the standard 12 doses. Over the period 1981–88, the filariasis control project in Samoa conducted three rounds of single-dose treatment with DEC covering the entire country and evaluated the long-term parasitological effects. This

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article summarizes the activities carried out during this 8-year period and the results obtained.

Materials and methods

Samoa consists of two main islands (Upolu and Savaii) and has a total population of about 160 000; endemic filariasis occurs, caused by diurnally subperiodic *W. bancrofti*, which is transmitted by *Aedes polynesiensis* and *A. samoanus* vectors. The filariasis control project was inaugurated in Samoa in 1981, when a nationwide mass drug administration (MDA) campaign using a single dose of DEC (6 mg/kg body weight) was adopted as a national strategy to control the disease. It was intended to cover the total Samoan population except infants under 1 year of age, pregnant women, sick people, and the very old.

Three MDAs were carried out: one each in 1982 (MDA-1), 1983 (MDA-2), and 1986 (MDA-3). Before the drug was administered, a population census was carried out in all villages in the country (>400) as well as in Apia, the capital, with the assistance of village women's committees. Based on the census results, the DEC tablets (or syrup for children aged 1–5 years) needed for each village were packed at the project office in Apia, distributed through local health centres, and administered to the inhabitants on the selected date, which was publicized in radio broadcasts. In each village a drug distribution team consisting of members of the women's committee confirmed that the tablets had been swallowed and kept treatment records. In Apia, three drug distribution booths were installed to distribute the drug to people who did not have village connections and those who were travelling. The treatment continued for 1–2 weeks after the selected date. The process was carried out under the close supervision of district nurses, doctors, and project staff.

To evaluate the effect of the MDAs, blood examinations using the 60- μ l blood smear method were carried out in 1981–82 (pre-MDA-1), 1982–83 (post-MDA-1), 1983–84 (post-MDA-2) and 1987–88 (post-MDA-3) on about 10 000 people in each instance. In the pre- and post-MDA-1 blood surveys, the same 27 villages were examined. For the post-MDA-2 and post-MDA-3 blood surveys, entirely different groups of villages were examined, consisting of 34 and 26 villages, respectively. The selection of villages was not random but designed to cover the whole country so that the results obtained would be representative. Compliance was excellent, and in most cases samples of blood from 80–90% of the villagers of all ages were obtained. To determine the mf density, we calculated the geometric mean of positive counts per 60 μ l.

Entomological studies were conducted at Vailu'utai, on Upolu. Samples of *A. polynesiensis*, the most important vector of *W. bancrofti* in Samoa, were collected over a period of 10 minutes at each of 12 indoor and 12 outdoor sites, as described by Samarawickrema et al. (15), on December 1981 to March 1982 (pre-MDA-1), November 1982 to January 1983 (post-MDA-1), and January to March 1984 (post-MDA-2). The mosquitos collected were dissected to determine the infection and infective rates.

Results

Coverage in the project censuses

The population censuses used for the MDAs were taken in each village by the filariasis control project with the assistance of the local women's committee. Comparison of the results with those obtained in the government census in 1981 and by district nurses, whose data were based on "household register" files, indicated that the coverage in the project was satisfactory. Detailed analysis using the data for 1983 revealed that relatively low registration rates (<80%) of the estimated national total were recorded for males aged 25–34 years in Upolu and for males aged 35–44 years in Savaii; also, females aged \geq 55 years in both islands had very poor registration rates (59–64%).

Treatment coverage

A total of 86.3% of the estimated Samoan population was covered in MDA-1, 83.8% in MDA-2, and 82.6% in MDA-3 (Table 1). Detailed analysis by sex and age based on the 1983 data revealed that <80% of children aged 0–4 years and females aged 15–24 years who were registered were treated and that the coverage of those aged \geq 55 years was particularly poor (46–68%). Of those who were not treated, 37–58% were absent or refused, and for both sexes such individuals were most commonly aged 15–24 years; the remainder were those deliberately excluded from treatment (Table 1).

Changes in microfilariae prevalence and density

Table 2 shows the changes in mf prevalence and density before and after the MDAs. The prevalences were adjusted using the standardized population, based on the 1981 national census. The decrease in prevalence was clear and steady for both sexes. The average prevalence dropped from 5.6% before, to 2.5% after the MDAs, i.e., a 55% reduction. The change in prevalence by sex and age is best illustra-

Table 1: Coverage in the three mass drug administration (MDA-1-3) campaigns with diethylcarbamazine citrate, and analysis of people who were not treated

	MDA-1 (1982)	MDA-2 (1983)	MDA-3 (1986)
National population	156 311	157 216	159 199
No. registered	149 150 (95.4) ^a	143 526 (91.3)	165 412 ^b (>100)
No. treated	134 878 (86.3)	131 732 (83.8)	131 507 (82.6)
<i>No. not treated</i>	<i>14 272</i>	<i>11 794</i>	<i>12 696</i>
No. of refusals/absentees	8272; 58.0 ^c	4387; 37.2	5457; 43.0
No. of infants (<1 year)	2139; 15.0	1808; 15.3	3371; 26.6
No. of pregnant women	1482; 10.4	1611; 13.7	2055; 16.2
No. of sick people	1575; 11.0	2495; 21.2	887; 7.0
No. very old	804; 5.6	1493; 12.7	926; 7.3

^a Figures in parentheses are the % of the national population.

^b Exceeds the national population probably because of multiple registration.

^c Figures in italics are the % of the number not treated.

Table 2: Changes in microfilariae (mf) prevalence and density

	Pre-MDA-1	Post-MDA-1	Post-MDA-2	Post-MDA-3
No. of individuals examined	10 361	9627	11 146	13 708
No. of positives	544	401	308	320
<i>Mf rate</i> ^a				
Male	8.0 (100) ^b	6.6 (83)	4.7 (59)	3.8 (48)
Female	3.2 (100)	2.6 (81)	1.6 (50)	1.3 (41)
Total	5.6 (100)	4.6 (82)	3.1 (55)	2.5 (45)
<i>Mf density</i>				
Male	23.1 (100)	9.9 (43)	11.2 (48)	9.1 (39)
Female	14.6 (100)	8.4 (58)	7.0 (48)	9.4 (64)
Total	20.2 (100)	9.4 (47)	9.8 (49)	9.2 (46)

^a Rate adjusted to the standardized population, based on the 1981 census.

^b Figures in parentheses are the % of the pre-MDA-1 level.

ted by comparing the pre-MDA-1 and post-MDA-3 data (Fig. 1). For both sexes and most age groups a clear reduction in prevalence was observed, particularly among males aged ≥ 50 years.

The mf density fell to about half the pre-treatment level after the first MDA, but thereafter remained almost constant.

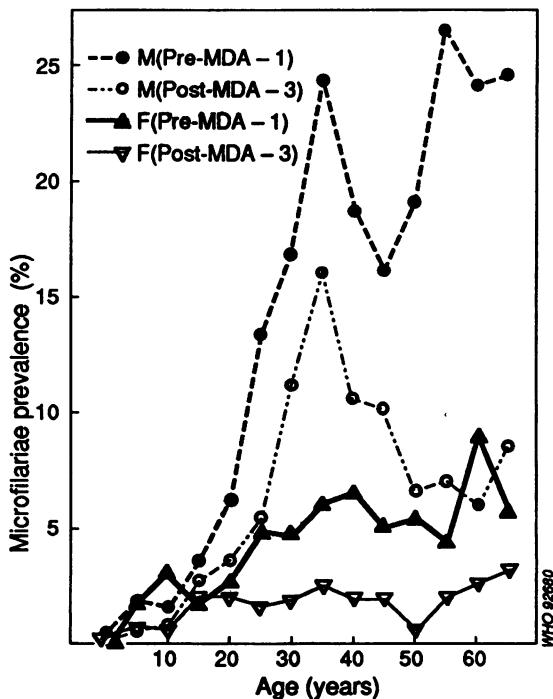
Changes in transmission potentials

The transmission potentials (infectivity indices of the total population) are shown in Table 3 (3). The mosquito infection rates at different microfilaraemia levels in 60 μ l of blood were calculated as reported by Kimura et al. (16), using transmission data provided by Samarawickrema et al. (17). The estimated number of mf positives in each blood survey was obtained by application of a truncated negative

binomial distribution (18, 19). The results indicated that the potential, which was 2.18 before treatment, reduced gradually to 0.67 after the MDAs (a 70% reduction).

The total number of mf in a given group of individuals (designated in Table 4 as the "transmission potential of the host" and calculated as the product of the number of mf positives in the group X mf density of these individuals) shows the relative importance of the group as a source of infection. Table 4 shows the potentials according to age group, calculated under the assumption that the four blood examinations were each performed on 10 000 villagers. The total potential fell gradually from 10 605.0 to 2147.3 (an 80% reduction), and among those aged ≥ 50 years the potential was significantly lowered by the MDAs, reducing the importance of old people as a source of infection.

Fig. 1. Change in microfilariae prevalence, by sex and age group, before and after single-dose treatment with DEC at 6 mg/kg body weight.



Entomological study

The mosquito biting density and the infection and infective rates are shown in Table 5. The infection and infective rates decreased, respectively, from 0.97% to 0.06% and from 0.28% to 0.02%, whereas the biting density (the number of bites per individual per hour) increased from 25.4 to 67.0

Discussion

In Samoa, two year-long, nationwide MDAs using DEC were carried out in 1965–66 and 1971 with a total dosage of 72–90 mg/kg spread over 12–18 doses. The effect of these MDAs was to reduce the mf prevalence from 20% to 0.24%. By 1979, however, the mf prevalence had reached 4–5%. This rapid increase is discussed below.

During 1974, a blood examination in Savaii using the 60- μ l blood smear method detected 64 mf positives out of 25 181 persons studied. In 1979, 3013 persons in Savaii were examined using the same method and 142 mf positives were detected. The age–sex-specific mf rates for 1974 and 1979 are shown in Table 6. If a constant rate of increase in mf

prevalence is assumed between 1974 and 1979, comparison of the prevalences in the same cohort in 1974 and 1979 permits the annual rate of increase to be estimated. The results obtained indicated that the rates in most age groups were very high (60–90%), i.e., that the increase in the mf prevalence in Samoa had been accelerating in the years before the MDAs (Table 6). The single-dose DEC mass treatment was then adopted as a national strategy for the following main reasons: a large-scale, multi-dose treatment schedule would not have been acceptable to the inhabitants after the two year-long MDAs, especially after the mf prevalence and clinical filariasis had been reduced to low levels; a DEC single-dose treatment of 6 mg/kg can reduce mf counts by 90% for at least 12 months (10); and low-density mf carriers who might arise with the single-dose treatment are unimportant in the transmission of filariasis (16).

In all the villages, most of the work associated with the MDAs was performed by villagers, especially by the members of women's committees. Some difficulties inevitably occurred in registration, such as the exclusion of people with illnesses and the very old. Despite this, more than 90% of the national population were registered and more than 80% were treated in each of the three MDAs. However, the original plan to conduct annual MDAs could not be carried out. Treatment coverage was poor for the age groups 0–4 years, 15–24 years (females only), and \geq 55 years. While the youngest and oldest age groups included many people who were excluded deliberately, the 15–24-year group appeared to have a disproportionately large percentage of absentees and refusals. A high migration rate was found for this group (E. Kimura, unpublished WHO report (WP)PDV/SMA/MPD/001).

Samples of blood were examined from 10 000 people in about 30 villages before and after each MDA. The villages were selected from all over the country and the results from the four surveys were considered to be comparable. Three single-dose DEC mass treatments at 6 mg/kg spaced over 1–3 years lowered the mf prevalence gradually from 5.6% to 2.5% (a 55% reduction). This reduction represents the therapeutic effect of DEC since there was no decrease in the mosquito biting densities. The effect of the MDAs was confirmed indirectly by the results of an independent mf prevalence study in neighbouring American Samoa, which included many Western Samoan migrant workers (27).

The infectivity index of the total population (the estimated % mosquito infection rate if everyone in a community is equally exposed to mosquito bites) is an accurate indicator of the transmission potential, since it includes parameters on the vector and the human host; the index fell from 2.18 to 0.67 (a 70%

Table 3: Infectivity indices of the total population of Samoa following the single-dose mass drug administration (MDA) campaigns

Microfilariae count	Mosquito infection rate (%) (A)	Estimated number of positives:			
		Pre-MDA-1 (B)	Post-MDA-1 (C)	Post-MDA-2 (D)	Post-MDA-3 (E)
1	7.6	43.6	44.3	33.1	37.8
2	10.3	28.2	28.4	21.3	24.2
3	12.4	21.5	21.5	16.1	18.3
4	14.1	17.6	17.5	13.1	14.8
5	15.6	15.1	14.9	11.1	12.6
6	16.9	13.2	13.0	9.7	10.9
7	18.1	11.8	11.5	8.6	9.7
8	19.2	10.7	10.4	7.8	8.7
9	20.3	9.8	9.4	7.1	7.9
10	21.2	9.1	8.7	6.5	7.2
11-20	28.9	66.7	61.1	46.1	50.5
21-30	34.7	44.0	37.4	28.4	30.1
31-40	39.5	32.9	25.9	19.8	20.4
41-50	43.6	26.1	19.1	14.7	14.7
51-60	47.3	21.4	14.6	11.3	10.9
61-70	50.7	18.0	11.4	8.9	8.3
71-80	53.8	15.4	9.0	7.1	6.5
81-90	56.7	13.4	7.3	5.8	5.1
91-100	59.4	11.7	5.9	4.7	4.0
101-200	81.0	66.0	24.2	19.7	14.9
201-300	97.1	25.6	4.4	3.9	2.1
≥301	100	22.3	1.2	1.2	0.4
Total number of positives		544	401	306	320
No. examined (F)		10 361	9627	11 145	13 708
Σ (A X No. positive) (G)		22 563	12 324	9586	9229
Infectivity index (G)/(F)		2.18	1.28	0.86	0.67

Table 4: Relative importance of age group as a source of infection and its change of importance following the single-dose mass drug administration (MDA) campaigns

Age group (years)	Transmission potential of the host: ^a			
	Pre-MDA-1	Post-MDA-1	Post-MDA-2	Post-MDA-3
1-9	531.9 (5.0) ^b	288.1 (7.4)	72.0 (2.7)	59.8 (2.8)
10-19	1344.8 (12.7)	439.9 (11.2)	296.7 (11.0)	445.1 (20.7)
20-29	1706.5 (16.1)	852.7 (21.8)	599.0 (22.3)	505.3 (23.5)
30-39	1959.1 (18.5)	691.1 (17.7)	960.5 (35.7)	554.8 (25.8)
40-49	1546.8 (14.6)	716.7 (18.3)	311.1 (11.6)	329.7 (15.4)
50-59	1927.9 (18.2)	638.4 (16.3)	285.7 (10.6)	118.3 (5.5)
≥60	1691.6 (16.0)	352.9 (9.0)	235.3 (8.7)	192.7 (9.0)
Total	10 605.0 (100)	3915.1 (100)	2691.1 (100)	2147.3 (100)

^a The total number of microfilariae in each age group.

^b Figures in parentheses are the % of the total number of microfilariae of each blood survey with 10 000 individuals.

Table 5: Mosquito infection and infective rates following the single-dose mass drug administration (MDA)/campaigns with diethylcarbamazine citrate

	Pre-MDA-1	Post-MDA-1	Post-MDA-2
No. of mosquitos collected	2004	2504	5245
Biting density ^a	25.4	38.3	67.0
No. dissected	1758	2332	5206
% infected	0.97	0.68	0.06
% infective	0.28	0.08	0.02

^a Per individual per hour.

reduction). The transmission potential of the host, which takes account of a human parameter, also fell by 80% for Samoa as a whole. The reduction in this potential was particularly clear among those aged ≥ 50 years. Following the MDAs, the 10–39-year age group replaced the over-40-year-old group as the most important source of infection. The entomological study was not extensive, but the clearly recognizable decrease in infection and infective rates supports the conclusion that the transmission potentials had been lowered significantly.

During the study, the treatment could not be evaluated clinically; however, the number of cases of clinical filariasis has decreased markedly in recent years in Samoa.

Ivermectin, a broad-spectrum antibiotic and potent antifilarial drug that has been used to treat onchocerciasis, is as effective as a full course of DEC in the treatment of lymphatic filariasis. A single dose of 20–200 $\mu\text{g}/\text{kg}$ quickly clears *W. bancrofti* mf and reduces the mf count by 50–95% when assessed 6 months after treatment (14, 20–22). It has therefore been suggested that a multi-dose treatment with DEC could be replaced by a single dose of ivermectin. However, several studies have reported that a single dose of DEC at 6 mg/kg reduces the mf count by 90% when determined 12 months after treatment (9, 10, 23). Cartel et al. compared single doses of DEC at 3 mg/kg and 6 mg/kg to a single dose of ivermectin (100 $\mu\text{g}/\text{kg}$) for the treatment of Polynesian *W. bancrofti* (24). The efficacy of the single dose of ivermectin was superior to that of DEC in terms of immediate mf clearance but not in terms of sustained mf decrease at 6 months. The single dose of DEC was successful in a mass treatment campaign in French Polynesia (25), and in the present study its long-term effect in the nationwide campaign was confirmed. Prophylactic use of a single dose has also given promising results in Kenya (26). Ivermectin is undoubtedly a very valuable drug, but the usefulness of DEC, which is cheap and has proved to be safe and efficient for over 40 years, must be recognized. Administration of a single dose of DEC annually would be valuable in

Table 6: Age–sex-specific percentage positive by survey during 1974 and 1979 in Savaii, and an estimate of the annual percentage increase in the proportion of the population that was positive over this period

Age group (years)	% mf rate in 1974 (X)		% mf rate in 1979 (Y)		Annual % increase ^a (Z)	
	M	F	M	F	M	F
0–4	0.00	0.00	0.00	0.00	—	—
5–9	0.00	0.00	0.91	1.32	—	—
10–14	0.12	0.00	1.32	1.07	—	—
15–19	0.52	0.00	2.76	2.03	87	—
20–24	1.00	0.39	7.87	1.02	72	—
25–29	1.97	0.75	13.46	4.49	68	63
30–34	2.33	0.57	23.08	8.75	64	63
35–39	0.56	0.51	16.95	10.98	49	81
40–44	0.63	0.00	18.00	10.67	100	84
45–49	1.97	0.00	19.15	2.86	98	—
50–54	1.69	0.29	22.03	0.00	62	—
55–59	2.78	0.00	16.67	5.00	58	77
60–64	0.68	0.00	20.59	9.38	49	—
≥ 65			18.42	0.00	93	—

^a Calculated using $Y = X(1 + Z/100)^5$.

areas where extensive multi-dose treatment cannot be conducted or repeated.

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Résumé

Efficacité à long terme d'un traitement de masse par une dose unique de citrate de diéthylcarbamazine contre *Wuchereria bancrofti* subpériodique diurne: 8 ans d'expérience aux Samoa

Le citrate de diéthylcarbamazine (DEC) est un antifilarien efficace, sans danger et très largement utilisé. Dans le traitement type contre *Wuchereria bancrofti*, on administre 12 doses de DEC à raison de 6 mg par kg de poids corporel, soit une dose totale de 72 mg/kg. Toutefois, l'emploi de ce schéma à doses multiples pose de considérables difficultés pratiques pour les campagnes de traitement de masse à grande échelle lorsque l'intérêt de la population décroît. Dans le Pacifique Sud, des traitements annuels par une dose unique de DEC de 6 mg/kg sont efficaces et se sont révélés beaucoup plus simples sur le plan opérationnel. Toutefois, l'effet à long terme de ce protocole de traitement n'avait pas encore fait l'objet d'une évaluation critique.

Aux Samoa, où les infestations à *W. bancrofti* subpériodique diurne sont en augmentation rapide, trois campagnes nationales de traitement de masse par une dose unique de DEC à raison de 6 mg/kg ont été réalisées en 1982, 1983 et 1986. Leurs effets ont été évalués par quatre enquêtes hématologiques utilisant un frottis sanguin de 60 µl en 1981, 1982, 1983 et 1987.

Le traitement de masse a couvert plus de 80% de la population estimée des Samoa (environ 160 000 personnes) lors de chaque campagne et a permis de réduire la prévalence des microfilaries de 5,3% avant le traitement à 2,4%, soit une réduction de 55%. L'indice d'infectiosité de la population totale (le taux estimé de transmission de l'infestation aux moustiques si tous les

membres d'une communauté sont également exposés aux piqûres) diminuait progressivement, passant de 2,18 avant le traitement à 0,67 après les trois traitements, soit une diminution de 70%.

Nos résultats montrent qu'un traitement par une dose unique de DEC répété à 1-2 ans d'intervalle permet de lutter efficacement contre le type pacifique de filariose de Bancroft. Ce schéma thérapeutique peut être appliqué dans les zones où un programme de traitement complet, comme celui qui est administré lors des campagnes de traitement type comportant 12 doses, ne peut être réalisé ou répété pour diverses raisons.

References

- Hewitt, R.I. et al. Experimental chemotherapy of filariasis. III. Effect of 1-diethylcarbamyl-4-methylpiperazine hydrochloride against naturally acquired filarial infection in cotton rats and dogs. *Journal of laboratory and clinical medicine*, **32**: 1314-1329 (1947).
- Hawking, F. A review of progress in the chemotherapy and control of filariasis since 1955. *Bulletin of the World Health Organization*, **27**: 555-568 (1962).
- WHO Technical Report Series No. 542, 1974, (*WHO Expert Committee on Filariasis: third report of the WHO Expert Committee*), pp. 9-13.
- Davis, A. & Bailey, D.R. The effect of salt medicated with diethylcarbamazine in bancroftian filariasis. *Bulletin of the World Health Organization*, **41**: 195-208 (1969).
- Sen, A.B. et al. Diethylcarbamazine medicated salt in the chemotherapeutic control of filariasis due to *Wuchereria bancrofti* in an open community. *Indian journal of medical research*, **62**: 1181-1189 (1974).
- Fan, P.C. et al. Control of bancroftian filariasis by common salt medicated with diethylcarbamazine in Lihyu District (Little Kinmen), Kinmen (Quemoy) Islands, Republic of China. *Annals of tropical medicine and parasitology*, **69**: 515-516 (1975).
- Wang, Z-S. et al. Filariasis survey by membrane filtration technique after mass DEC administration. *Chinese medical journal*, **95**: 653-654 (1982).
- Merlin, M. et al. 25 ans de campagnes de masse antifilariennes en Polynésie française. *Médecine tropicale*, **36**: 631-640 (1976).
- Laigret, J. et al. Progrès dans l'emploi de la diéthylcarbamazine en chimiothérapie de la filariose lymphatique à *Wuchereria bancrofti* var. *pacifica*: la méthode des doses espacées. *Bulletin de l'Organisation mondiale de la Santé*, **56**: 985-990 (1978).
- Kimura, E. et al. The efficacy of annual single-dose treatment with diethylcarbamazine citrate against diurnally subperiodic bancroftian filariasis in Samoa. *Bulletin of the World Health Organization*, **63**: 1097-1106 (1985).
- Aziz, M. A. et al. Efficacy and tolerance of ivermectin in human onchocerciasis. *Lancet*, **2**: 171-173 (1982).

12. **Pacqué, M. et al.** Safety of and compliance with community-based ivermectin therapy. *Lancet*, **335**: 1377–1380 (1990).
13. **Greene, B.M. et al.** A comparison of 6-, 12-, and 24-monthly dosing with ivermectin for treatment of onchocerciasis. *Journal of infectious diseases*, **163**: 376–380 (1991).
14. **Ottesen, E.A. et al.** A controlled trial of ivermectin and diethylcarbamazine in lymphatic filariasis. *New England journal of medicine*, **322**: 1113–1117 (1990).
15. **Samarawickrema, W.A. et al.** Natural infections of *Wuchereria bancrofti* in *Aedes (Stegomyia) polynesiensis* and *Aedes (Finlaya) samoanus* in Samoa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **81**: 124–128 (1987).
16. **Kimura, E. et al.** Low-density microfilaraemia in subperiodic bancroftian filariasis in Samoa. *Bulletin of the World Health Organization*, **63**: 1089–1096 (1985).
17. **Samarawickrema, W.A. et al.** Filariasis transmission in Samoa I. Relation between density of microfilariae and larval density in laboratory-bred and wild-caught *Aedes (Stegomyia) polynesiensis* (Marks) and wild-caught *Aedes (Finlaya) samoanus* (Gruenberg). *Annals of tropical medicine and parasitology*, **79**: 89–100 (1985).
18. **Pichon, G. et al.** Etude de la distribution des numérations microfilariennes dans les foyers de filariose lymphatique. *Tropenmedizin und Parasitologie*, **31**: 165–180 (1980).
19. **Kimura, E. et al.** Epidemiology of subperiodic bancroftian filariasis in Samoa 8 years after control by mass treatment with diethylcarbamazine. *Bulletin of the World Health Organization*, **63**: 869–880 (1985).
20. **Diallo, S. et al.** Dose-ranging study of ivermectin in treatment of filariasis due to *Wuchereria bancrofti*. *Lancet*, **1**: 1030 (1987).
21. **Kumaraswami, V. et al.** Ivermectin for the treatment of *Wuchereria bancrofti* filariasis. Efficacy and adverse reactions. *Journal of the American Medical Association*, **259**: 3150–3153 (1988).
22. **Roux, J. et al.** Etude de l'ivermectine pour le traitement de la filariose lymphatique due à *Wuchereria bancrofti* var. *pacifica* en Polynésie française. *Bulletin de la Société de Pathologie exotique*, **82**: 72–81 (1989).
23. **Rachou, R.G. & Scaff, L.M.** [Reduction in *Wuchereria bancrofti* microfilaraemia with Hetrazan in treatment schemes of different duration]. *Revista brasileira de malariologia e doencas tropicais*, **10**: 303–326 (1958) (in Portuguese).
24. **Cartel, J.-L. et al.** Double-blind study on efficacy and safety of single doses of ivermectin and diethylcarbamazine for treatment of Polynesian *Wuchereria bancrofti* carriers. Results at six months. *Tropical medicine and parasitology*, **42**: 38–40 (1991).
25. **Laigret, J. et al.** Chimiothérapie de masse par la diéthylcarbamazine en doses espacées: effets obtenus à Tahiti sur la microfilarémie à *Wuchereria bancrofti* var. *pacifica*. *Bulletin de l'Organisation mondiale de la Santé*, **58**: 779–783 (1980).
26. **Wijers, D.J.B. et al.** Diethylcarbamazine prophylaxis against bancroftian filariasis given by a member of the local community in Kenya. *Annals of tropical medicine and parasitology*, **82**: 411–412 (1988).
27. **Reid, E.C. & Kimura, E.** Microfilaria prevalence of diurnally subperiodic *Wuchereria bancrofti* among people having a medical check-up in American Samoa in the past 17 years. *Journal of tropical medicine and hygiene*, (in press).