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The impact of 34 years of massive DEC chemotherapy on *Wuchereria bancrofti* infection and transmission: the Maupiti cohort

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Summary Semi-annual mass DEC chemotherapy combined with vector control at the beginning of the programme, has been administered on the remote island of Maupiti (French Polynesia) since 1955 (except two periods in 1960–67 and 1970–74). The results of two surveys in 1985 and 1989, reporting 0% microfilaraemia, led to the hope that the eradication of lymphatic filariasis had been achieved. We combined parasitological criteria (microfilaraemia by membrane filtration), immunological (antigenaemia and serum levels of specific IgG antibodies) and molecular (PCR-based evaluation of infection in mosquitoes) techniques and found only good control of the parasite: We found residual microfilaraemia in 0.4% of the sample (mean level in carriers: 101.2 mf/ml), antigenaemia in 4.6% (mean level in positive persons: 714.4 units/ml) and specific IgG in 21.6% (including in one very young child). In addition, an infection rate of 1.4% was calculated in the *Aedes polynesiensis* vector population. These data, obtained in 1997 just before a hurricane, were partially confirmed in 1999 (0.1% of infection rate in the vector). Together with the possibility of some resistance to DEC, various epidemiological factors critical for the eradication of lymphatic filariasis are discussed.

keywords lymphatic filariasis, *Wuchereria bancrofti*, diethylcarbamazine, control

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Introduction

From 1949 to 1953, the 'Pacific Tropical Disease Project' between the Institut de Recherches Médicales de Polynésie Française, now called the Louis Malardé Medical Research Institute, and the University of California, Los Angeles set the standard for control of lymphatic filariasis in the South Pacific. With the exception of the 1960–67 and the 1970–74 periods, mass diethylcarbamazine chemotherapy of 6 mg/kg every 6 months (DEC 6) combined with vector control (DDT 1955–57 and destruction of larvae 1955–70), was administered over more than 30 years on the island of Maupiti. The results of two recent surveys, reporting 0% microfilaraemia based on the blood smear method, led to the hope that lymphatic filariasis had been eradicated.

The geographical situation of Maupiti, which experiences very little migration to and from neighbouring islands, offers a unique opportunity to evaluate the long-term effect of a DEC-based control strategy. This study combines parasitological indicators (mf and microfilarial density), immunological (Ag and serum levels of specific IgG antibodies) and molecular (PCR-based evaluation of infection in mosquitoes) techniques (Nicolas 1997; Ottesen *et al.* 1997), to evaluate whether eradication of this infection was attained.

Patients and methods

Study area

The target population of this investigation were all inhabitants of Maupiti (Figure 1), a small (13.5 km^2 for the inhabited centre) and remote island located 315 km NW of Tahiti and 50 km from Bora-Bora, with difficult access from the sea. The population is very stable (963 inhabitants in 1988, 1127 in 1996), with the main activities being watermelon culture and copra harvesting Ministère des Archipels 1997), on the central and *motu*

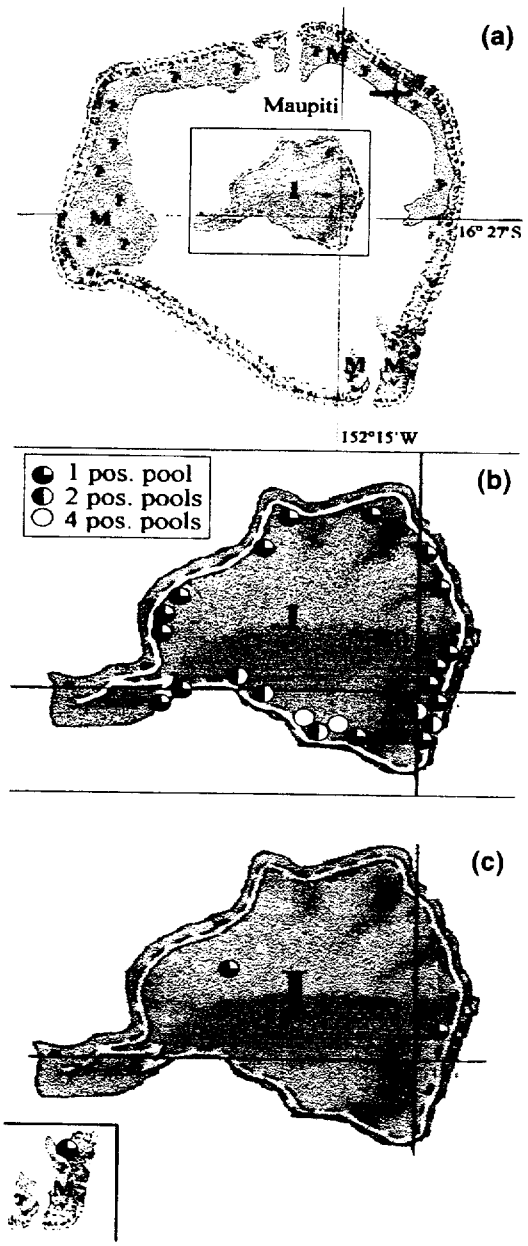

Figure 1 Map of Maupiti island (Society archipelago, French Polynesia. a, M: *Motu*, small sandy islands mainly devoted to agriculture. Circles indicated positive sites for infected mosquitoes. b, 1999 survey. c, 1999 survey as determined by PCR-based pool screening (see text for explanations). Scale: 1 cm = 1 km. I: Island, main island where most of the inhabitants of Maupiti live, in comparison to the surrounding flat islets called Motu where there are some agricultural activities.

(surrounding islets) islands, respectively (Figure 1). The Maupiti cohort, representing one of the historical endemic foci of lymphatic filariasis in French Polynesia (Laigret *et al.* 1978a), has been followed for more than 40 years by the same team. The Maupiti study was part of a larger Institut Malardé epidemiology project, recently sponsored by the World Health Organization (WHO). Migratory movements are limited in this area, hence the risk of re-infestation by recently arrived migrants is considered to be very low. As a result of the social and political mobilization initiated at the beginning of this control programme, coverage of about 85% of the target groups was regularly achieved (March *et al.* 1960; Laigret *et al.* 1978a).

Operational activities were undertaken by local infirmary staff and supervised by experts from the Malardé Institute (during the 1955–83 period) and the Ministry of Health (since 1984). In November 1997, just 1 week after the epidemiological survey, intense rainfall and flooding caused by the hurricane Osea, which ripped through the Society archipelago, destroyed 80% of the houses on Maupiti.

Pretreatment parasitological examinations

Information on previous treatment for filariasis and prevalence of infection was obtained from technical reports presented to the head of the Malardé Institute after each epidemiological survey (Laigret *et al.* 1978a; Bezannier & Fagneaux 1982; Perolat & Roux 1986).

The control programme organized by the Malarde Institute

DEC 6 mg/kg has been available for monthly (1955–59) or bi-monthly (1968 and 1969) mass chemoprophylaxis and, with the exception of 11 years of selective treatment of positive carriers (every 6 months from 1960 to 1964, bi-monthly from 1965 to 1967 and from 1970 to the beginning of 1974), mass chemoprophylaxis has been performed every 6 months since 1974 (Laigret *et al.* 1978a,b, 1980; Perolat & Roux 1986). This represents a 34-year DEC-based mass campaign against lymphatic filariasis (Figure 2). Mass treatment of the whole population was offered free of charge and participation in the campaigns and the present study was entirely voluntary. The study design was reviewed by the Polynesian Ministry of Health and found to comply with ethical guidelines for research involving human subjects.

Vector control was organized parallel to morbidity control. Outdoor and indoor spray treatments with 2% aqueous solution of DDT took place until 1957 (Merlin *et al.* 1976), followed by antilarval mechanical destruction of peridomestic foci (mainly coconuts on the ground,

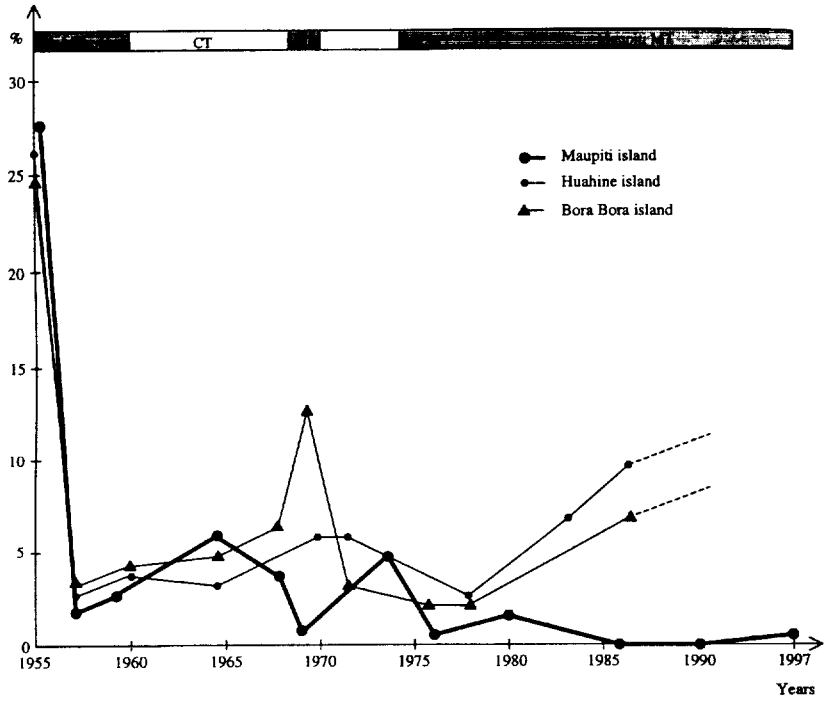

Figure 2 Compared evolution of microfilaraemia in three islands of the Society archipelago, after continuous (Maupiti) or stopped (*Bora-Bora* and *Huahine*) DEC chemoprophylaxis after 1978. MT, mass treatment with DEC 6 mg/kg; CT, carriers treatment with DEC 6 mg/kg (see text for different regimens), Maupiti-MT, mass treatment exclusively in Maupiti island.

which are the preferred ecological niche for the only vector *Aedes polynesiensis*) and repeated sanitary education campaigns until 1970.

Parasitological examinations in 1980, 1985 and 1989

Rapid screening, using finger-prick, of representative samples (650, 700 and 800 inhabitants, respectively) was performed early in 1980, 1985 and 1989 by the same team. All observations were double blinded and conducted by two independent observers. The results are presented as mean, standard deviation.

Evaluation of the impact of the programme in 1997 and 1999

In November 1997, about 98% of the target population was enrolled in a complete epidemiological survey. A total of 999 sera taken from inhabitants over the age of 2 years (mean age: 27.3, 20.2 years) were tested for microfilaria by membrane filtration technique, and for specific IgG levels by ELISA (Chanteau *et al.* 1994a; Simonsen *et al.* 1996). Another set of 56 finger-prick samples from infants under 2 years, from whom a venous blood sample could not be collected, was also analysed for specific IgG. The results are presented on the global sample of 1055 sera. We also analysed the Og4C3 Ag (Weil *et al.* 1987; Chanteau *et al.* 1994b; Simonsen *et al.* 1996), using a commercial (TropBio, Townsville, Australia) enzyme-linked immunosorbent assay (ELISA), on the larger sample of 997 sera.

A. polynesiensis mosquitoes (2994 in 1997 and 3104 in 1999), captured by an entomological team in the vicinity of all the habitations indexed on the reference map of the island (Figure 1a), were analysed with a PCR-based pool screening method using *W. bancrofti*-specific primers (Chanteau *et al.* 1994a; Nicolas *et al.* 1996; Nicolas & Plichart 1997).

Results

Pretreatment endemicity levels

The data confirm the good results noted during the first years of mass campaigns against filariasis (Table 1). Parallel to the evolution of prevalence, the density of microfilariae in carriers decreased from 234.5 mf/ml in 1955 to 13.0 mf/ml in 1959 before rising again after the carrier treatment period to 151.0 mf/ml in 1966 and 152.0 mf/ml in 1974. A rapid decline occurred (30.1 mf/ml in 1977, 0.5 mf/ml in 1980 and 0.0 mf/ml in 1985 and 1989) after the reinstatement of mass treatment, in contrast to the situation on neighbouring islands, where this control strategy was interrupted

Table 1 Evolution of endemic lymphatic filariasis in Maupiti island (Society archipelago, French Polynesia) from 1955 to 1999

Year Examined	Number (%)	Prevalence (mf/ml)	Density
1955	514	26.65	234.5
1958	503	2.18	76.5
1959	582	2.74	13.0
1960	610	2.29	ND
1961	631	1.26	8.7
1962	620	1.45	6.7
1965	502	5.37	87.4
1966	557	5.92	151.2
1968	551	4.14	35.7
1969	530	0.75	16.2
1974	598	5.01	152.1
1977	653	0.30	30.0
1980	650	1.60	0.5
1985	700	0.00	0.0
1989	800	0.00	0.0
1997	998	0.40	105.0
1999*	(41)*	0.20*	26.5*

*1999 data were obtained on a small sample (see text for explanation). ND, not determined.

(Figure 2). In 1989, 66 schoolchildren aged 9–11 years were examined for specific IgG and revealed 12.0% positivity.

Parasitological and immunological indices

The proportion of microfilaraemic individuals in the samples fell to 1.6% in 1980 and 0.0% in 1985 and 1989 (Laigret *et al.* 1978a; Bezannier & Fagneaux 1982; Perolat & Roux 1986). The 1997 survey revealed that four of 999 (0.4%) tested inhabitants were low-level carriers (mean mf 101.2, 86.0 mf/ml). Two of these four individuals were young men who had arrived less than 2 years previously from an endemic area (Raiatea island, mean prevalence about 20%) but the other two had been living in Maupiti all their life and had frequently been treated with DEC. Three of these microfilaraemic individuals were followed-up in 1999, and only one had become negative (microfilaraemia of the two positives: 51 mf/ml and 2 mf/ml). In addition, 46 inhabitants (4.6% of a sample of 997 sera, mean age: 48.8, 20.7 years) had positive Ag (mean level: 714.4, 609.6 units) and 227 (21.6% of a sample of 1055 sera) had a carried specific IgG (mean level: 2361.5, 3454.9 UI/ml). Remarkably, one infant under 2 years tested positive in the IgG assay (1159 UI/ml). Of these 46 antigen-positive inhabitants, 31 were re-examined in 1999 and 64.5% ($n = 20$) were still positive (mean level: 867.6, 435.5 units).

Entomological indices

The population of *A. polynesiensis* was relatively stable before and after the hurricane period (8.60 and 7.80 mosquitoes/man/spot in 1997 and 1999, respectively), whereas the population of *A. aegypti*, as estimated on a limited sample (107 and 292 mosquitoes captured in 1997 and 1999, respectively) increased significantly (0.31 and 0.74 mosquitoes/man/spot in 1997 and 1999, respectively; $P < 0.001$). Of 96 pools of 30 mosquitoes, each analysed by PCR, 34 were found to be positive in 1997. Using specialized software (Poolscreen, Katholi *et al.* 1995), we calculated a 1.4% global prevalence in the vector population with a 95% CI 1.00–2.03). Localization of positive spots on the island apparently bears no relationship to the density of houses or population (Figure 1b). In 1999, a sample of 108 pools of 30 mosquitoes was analysed following the same protocol, and only three were positive (0.1% of prevalence, 95% CI 0.02–0.3), including one on a *motu* (Figure 1c).

Discussion

Various field studies in French Polynesia (March *et al.* 1960; Merlin *et al.* 1976; Laigret *et al.* 1978a,b, 1980) and elsewhere (Ottesen 1994; WHO 1994; Meyrowitsch & Simonsen 1998) have proved that *W. bancrofti* transmission can be greatly reduced if the recommended strategies (DEC alone or in combination with ivermectin) are properly implemented. Establishing a surveillance programme with standardized tools, such as ELISA-based circulating antigen assays (Weil *et al.* 1987; Chanteau *et al.* 1994b; Simonsen *et al.* 1996), measuring specific IgG in the absence of any confounding diseases including other filariases (Chanteau *et al.* 1994a; Simonsen *et al.* 1996), and PCR-based evaluation of prevalence in mosquitoes (Chanteau *et al.* 1994c; Nicolas *et al.* 1996; Nicolas & Plichart 1997), provides quantifiable data of monitoring progress on the road to eradication of this parasitic disease (Ottesen *et al.* 1997; Nicolas 1997).

Considering this, it is important to highlight that on a remote island, where a DEC-based mass chemotherapy was in place for three decades, eradication could not be achieved. Inhabitants, including young children, are still infected by the parasite (about 4% are microfilaraemic and have circulating Ag) and a non-negligible proportion (1.4% before the hurricane, 0.1% after) of *Aedes polynesiensis* is still implicated in low-level continuous transmission. A comparable situation prevails in Western Samoa, where *W. bancrofti* is locally transmitted by *A. polynesiensis* and *A. samoanus*. After 7 years of mass DEC administration, the prevalence fell from 19.1% (in 1965)

to 0.2% (in 1972) but low-level microfilaraemia persisted in the following years, leading to renewed transmission (Suzuki & Sone 1975), a rise in prevalence and reappearance of acute clinical manifestations (Kimura *et al.* 1985).

Three possible explanations for the failure of eradication can be put forward. One has to do with increased efficiency of the vector *A. polynesiensis* in low-level microfilaraemics (Rosen 1955; Carme & Laigret 1979; Perolat & Roux 1986; Southgate 1992); the second with some documented cases of prolonged longevity of adult parasites (Carme & Laigret 1979; Vanamail *et al.* 1996) and the third with resistance of *Wuchereria* to DEC as suggested by Brazilian studies, with a significant proportion of adult worms insensitive to DEC at doses of 6 mg/kg or more (Figueiredo-Silva *et al.* 1996; Noroes *et al.* 1997), a problem which was supposed to be overcome by the use of yearly repeated single doses of DEC in community-based control programmes (WHO 1994). In fact, DEC alone cannot apparently interrupt the transmission of lymphatic filariasis in hyperendemic areas because elimination of all adult worms seems to be an out-of-reach goal for individual DEC therapy. DEC-based mass campaigns not only aimed at eradicating filariasis, but also – as for schistosomiasis and most of the helminth infection control programmes – at stabilizing endemicity at a low level in order to limit its public health importance (Merlin *et al.* 1976).

In addition to these limiting factors, other unfavourable conditions such as low drug coverage and human population movements play a role. All in all, the potential of DEC alone to eradicate lymphatic filariasis may be lower than predicted and studies using an additive macrofilaricide drug (Addiss *et al.* 1997; Ismail *et al.* 1998) must urgently be conducted in areas with differing intensities of transmission and vectorial competence to see whether they invalidate the negative trend presently recorded in French Polynesia. Two recent studies suggest that albendazole could be a viable macrofilaricidal drug (Addiss *et al.* 1997; Ismail *et al.* 1998) to be added to routine schedules (DEC or IVM) for the eradication of lymphatic filariasis in endemic areas. Our results are relevant to the need for mass campaigns using this combination of drugs as the major strategy of the global eradication initiative recently launched by WHO (1998).

In May 1997, the 50th World Health Assembly resolved to make the eradication of lymphatic filariasis in the world a priority (WHO 1998). A regional plan to eradicate lymphatic filariasis as a public health problem (PacELF for the Pacific region) by the year 2010 was formulated in conjunction with the WHO and the Secretariat of the Pacific Community. French Polynesia is part of this regional programme and Maupiti island is one of the three sentinel zones to be followed. One byproduct of these surveys was the discovery of an increase of the *A. aegypti* population after the hurricane, in contrast to *A. polynesiensis*. This is important in terms of dengue surveillance in the Pacific and probably linked to the programme of building wind-resistant houses launched by the local authorities and also to the fact that hurricane-dilapidated houses provided favourable ecological niches. Knowledge of such insidious risk factors is important for public health on all Pacific islands.

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