Dengue 1 epidemic in French Polynesia, 1988–1989: surveillance and clinical, epidemiological, virological and serological findings in 1752 documented clinical cases

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Abstract

An epidemic of dengue 1 occurred in French Polynesia in December 1988 and June 1989. This paper records (i) the trend of the outbreak and its surveillance and (ii) the clinical, epidemiological and virological data obtained from 1752 documented cases. The epidemic reached its peak in February in Tahiti Island, 7 weeks after its recognition. Among 6034 suspect cases reported by sentinel physicians, 60·3% were <20 years old. The illness was classical dengue. No fatality or case of dengue haemorrhagic fever/dengue with shock syndrome was reported. Of 4792 patients subjected to laboratory testing, 41% were confirmed as positive. The serological attack rate was *c.* 40%. The estimated number of dengue infections in the Windward Islands was about 20 000. Transmission was associated with *Aedes aegypti*. Study of documented cases showed a higher confirmation rate in both the civilian population <15 years old (46·5%) and the susceptible French military population (47·6%) than in older civilians (31·1%, $P<0·05$). Furthermore, primary dengue infections were predominant in both of the first 2 groups. The diagnosis was mostly confirmed (i) by virus isolation on day <5 of illness and (ii) by detection of immunoglobulin (Ig) M on day ≥5 of illness. The study showed that adequate surveillance of an epidemic requires both clinically and laboratory-based systems.

Introduction

French Polynesia is situated in the south Pacific ocean and consists of 5 archipelagoes (Society, Tuamotu, Gambier, Austral and Marquesas Islands), comprising 120 islands of which only 66 are inhabited. Most of the population is distributed in the Society archipelago which is subdivided into the Windward and Leeward Islands. Tahiti, the largest island of the Windward group, contains the capital, Papeete. The total population was 188 814 in 1988: 145 000 in Tahiti, of whom 79·1% live in the Papeete agglomeration. About 2300 inhabitants live in French Polynesia on a temporary basis. In all areas the climate is hot and tropical. A hot rainy season from November to April alternates with a cooler, drier season from May to October. The annual average temperature in Tahiti is 25·7°C.

All 4 dengue virus serotypes have occurred in epidemic form during the last 50 years in French Polynesia: dengue 1 in 1944 and 1975–1976, dengue 2 in 1971, dengue 3 in 1964 and 1969, and dengue 4 in 1979. From 1979 to 1988, transmission of dengue 4 continued at a very low level (CHUNGUE *et al.*, 1989b).

In December 1988, dengue virus 1 was isolated from a 15 years old child who presented with a dengue-like illness. The patient lived in a suburb of Papeete. Subsequent survey showed that 2 family contacts possessed immunoglobulin (Ig) M anti-dengue antibodies. Based on the dates of the past dengue 1 epidemics (1944 and 1975–1976), the susceptible population in the Windward Islands was estimated to be about 45 000, and consisted mostly of children born after 1979, some of those born in 1977–1978, and people living on a temporary basis. Previous serological study conducted in 1987 in Tahiti showed that 83·1%, 66·6%, 24·2% and 7·4% of children aged 15–19, 10–14, 5–9 and 0–4 years, respectively, had dengue antibodies for at least one serotype (CHUNGUE *et al.*, 1989b).

In this paper, we describe the trend of the epidemic and the various means of surveillance as well as clinical, epidemiological, virological and serological data obtained from 1752 clinical cases over the period December 1988 to June 1989.

Materials and Methods

Surveillance of the epidemic

As soon as the outbreak was recognized, public health measures were instituted. Information messages were delivered on vector control, on minimizing risk of infection, and on the procedure to be adopted in the event of illness. Ultra-low volume (ULV) spraying of urban areas with malathion was started in the last week of 1988, and maintained until mid-March 1989.

Weekly data were collected from December 1988 to June 1989, and overall indicators were available except for the number of declared suspect cases during weeks 17–19 (1989).

The surveillance of the epidemic involved the following operations. (i) Weekly reporting, by 25 sentinel physicians located throughout French Polynesia, of the number of clinically suspect cases, their age and their home address (a case of dengue was defined as a patient who presented with a sudden onset of febrile illness with any 2 of the following symptoms: headache, myalgia, arthralgia, rash or haemorrhagic manifestations). (ii) Virological and serological diagnosis (the weekly number of requests for laboratory testing and the weekly confirmation rate were measured). (iii) Estimation of the serological attack rate. Firstly, a cohort of 25 non-immune French soldiers, enrolled in August 1988 as part of our routine surveillance activity, had blood taken the day after their arrival, in December 1988 and February and April 1989. Clinical data and the presence of anti-dengue IgG and/or IgM antibodies were recorded for each individual. Secondly, antibody prevalence in April 1989, in a random sample of children aged 0–9 years, was compared with that obtained in a similar sample and extrapolated back to a pre-epidemic value in December 1988 (using an estimated annual antibody acquisition rate of 2·95%; CHUNGUE *et al.*, 1989b). Thus, the attack rate was assumed to be equivalent to at least the difference between the seroprevalence rate observed before and after the epidemic. (iv) Virological survey investigations on mosquitoes collected in 5 sentinel stations, located in urban and semi-urban areas of Papeete. Detailed entomological studies will be presented elsewhere.

Clinical specimens

Blood samples were collected from 4792 patients with a clinical diagnosis of dengue. Sera were stored at −80°C for virus assays and at −20°C for serological tests. Total leucocyte and platelet counts and haematocrit determinations were done using an automated counter (Coultronics, France).

The group of documented cases referred to in this study consisted of 1752 patients from whom completed questionnaires containing demographic and clinical in-

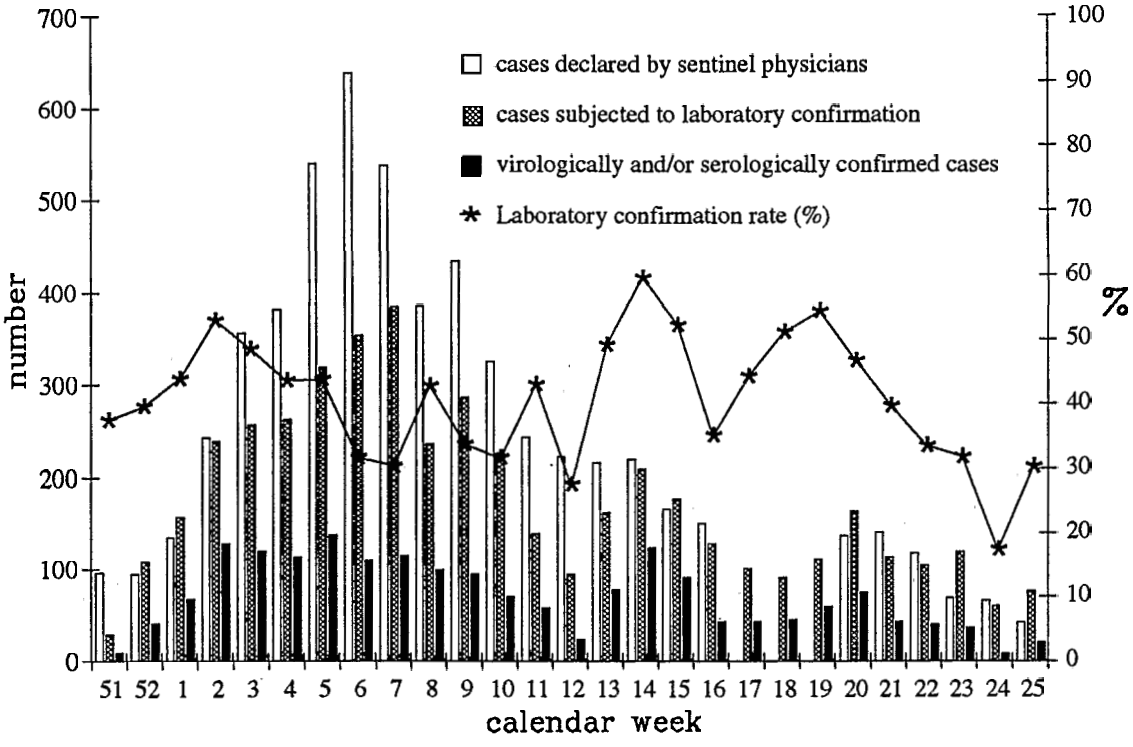

Fig. 1. Weekly surveillance of dengue 1 epidemic according to different indicators.

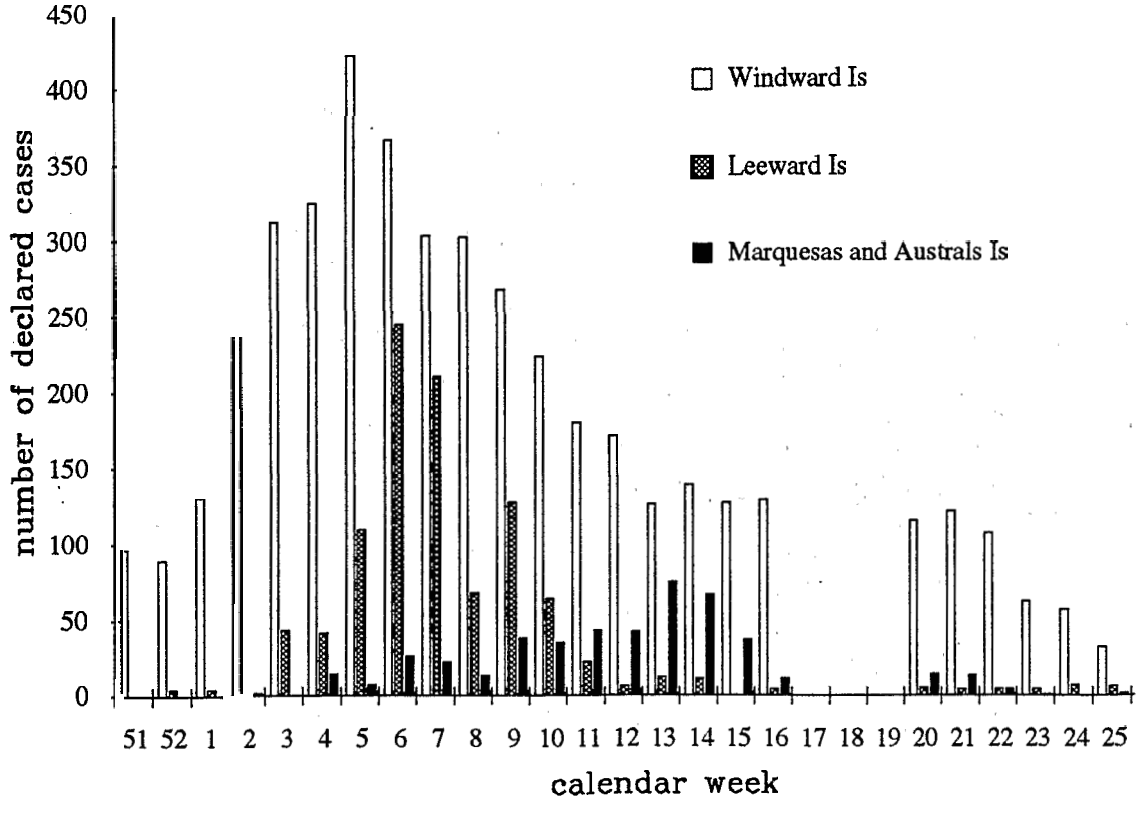

Fig. 2. Weekly number of clinically suspect cases of dengue 1 reported by sentinel physicians, according to island group.

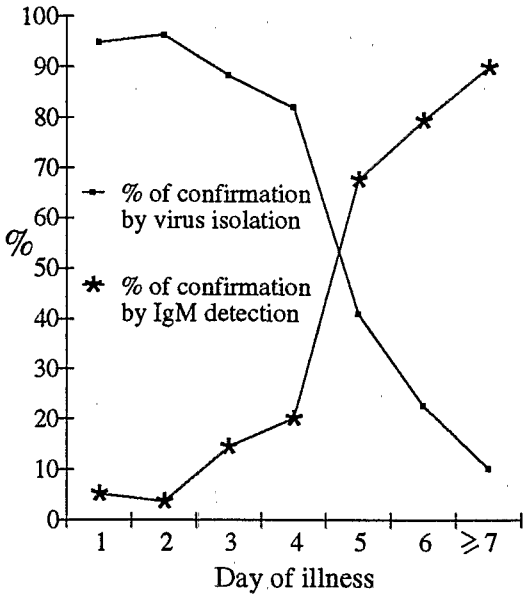

Fig. 3. Percentages of confirmation of dengue 1 diagnosis by virus isolation or detection of anti-dengue IgM antibodies according to day of illness (virus isolation was not attempted in 38 serum specimens collected after 12 days of illness).

Table 1. Distribution of clinically suspect cases of dengue reported by sentinel physicians by island group

Island group	No. of declared cases	General population	Incidence rate (%)
Windward Is.	4483	140341	3·2
Leeward Is.	1048	22232	4·7[b]
Marquesas and Austral Is.	503	13967	3·6[b]
Total	6034	175540[a]	3·4

[a]Total population except Tuamotu and Gambier Is.
[b]Significantly different from the Windward island incidence rate ($P<0·01$).

Table 2. Estimation of serologically confirmed dengue attack rate by comparison of dengue antibody prevalence in two sentinel groups before and after the epidemic

Susceptible population	Anti-dengue IgM and/or IgG prevalence (%)	Attack rate estimates (%)
Cohort of dengue non-immune adults		
French soldiers (n=25)		
December 1988	0·00	
April 1989	44·00	44·00
Children born 1980–1985		
April 1987 (n=170)	11·76[a]	
December 1988 (pre-epidemic estimated value)	16·67[b]	
April 1989 (n=109) (post-epidemic sample)	57·79	41·12

[a]Baseline data (CHUNGUE *et al.*, 1989b).
[b]Estimate calculated by extrapolation based on previous data that showed an anti-dengue antibody acquisition rate of 2·95% per year in children aged 2–7 years in April 1987 (CHUNGUE *et al.*, 1989b).

formations were obtained. The documented cases were subsequently grouped into civilian and military populations (the latter including family members).

Virus isolation

Virus assays were attempted by inoculation of the first serum samples into clone C6/36 of *Aedes albopictus* cells using 24-well plates (Nunclon®, 2 cm^2) and maintained in RPMI 1640 medium that contained 2% heat-inactivated foetal calf serum and antibiotics. Because of toxicity to mosquito cells, samples diluted 1:40 in 200 µl of the maintenance medium were used. After incubation at 30°C for 7–10 d, the cells were screened by an indirect fluorescent antibody test (IFAT) using dengue 2 hyperimmune ascitic fluid (American Type Culture Collection) and fluorescein isothiocyanate-conjugated sheep anti-mouse IgG (Diagnostics Pasteur). Subsequent identification was achieved by IFAT using serotype-specific monoclonal antibody (HENCHAL *et al.*, 1983).

Female adult *Ae. aegypti* and *Ae. polynesiensis* were captured using the human bait collection technique (BONNET & CHAPMAN, 1958) and starved for 24–48 h before being killed by freezing. Pools of up to 50 mosquitoes were constituted according to species and locations. To each pool of mosquitoes were added 100 µl per mosquito of chilled phosphate-buffered saline (0·05 M, pH 7·6) containing 20% heat-inactivated foetal calf serum and antibiotics. The material was then ground using an appropriately sized tissue grinder in an ice bath and centrifuged at 800*g* for 20 min at 4°C. The clarified homogenate was processed similarly to serum specimens at a dilution 1:10 in maintenance medium.

Serological methods

IgM capture enzyme-linked immunosorbent assay (ELISA). This was performed as previously described (CHUNGUE *et al.*, 1989a), using 4 serotype antigens. For routine serodiagnosis of dengue fever, patients with an IgM reciprocal titre ≥400 for any of the 4 antigens were considered as serologically confirmed cases. For serological surveys, all subjects with titres ≥100 were considered positive since IgM may persist at a low level (<400) for 90 d or more after infection.

IgG ELISA. The test was performed as previously described (CHUNGUE *et al.*, 1989b). A reciprocal titre ≥100 for any of the 4 antigens tested was considered as IgG positive.

Haemagglutination-inhibition tests (HI) and serological classification. The HI titres were determined by the method of CLARKE & CASALS (1958), using 4–8 haemagglutinin units of dengue 1 and 2 viral antigens per test. A reciprocal titre <10 was considered as negative.

Classification as primary or secondary infections was attempted in a random sample of 329 documented cases from whom virus had been isolated from acute serum. Thus, patients with a negative HI test for both dengue 1 and 2 antigens in their acute serum were classified as primary infections. Patients with a positive HI test for either antigen were considered as having had a secondary infection.

Statistical analysis

The χ^2 test was used for analysis of differences between proportions.

Table 3. Frequency of clinical symptoms observed in 701 laboratory-confirmed dengue patients

Clinical symptoms	Frequency (%)
Fever/headache/myalgia	98·3
Adenopathies	22·9
Macular rash	20·9
Digestive signs (vomiting, nausea, diarrhoea)	19·2
Taste alterations	16·1
Pruritis/paresthesia	9·9
Haemorrhagic signs (epistaxis, petechia, purpura)	5·1
Hepatalgia/hepatomegaly	5·0
Papular rash	4·7

Results

Surveillance of the epidemic using different indicators

The weekly number of (i) clinically suspect cases reported by sentinel physicians, (ii) patients subjected to laboratory confirmation by medical practitioners, whether sentinel or not, (iii) laboratory confirmed cases, and (iv) the weekly laboratory confirmation rate, are

Table 4. Numbers and percentages of cases confirmed in the laboratory by age group in civilian and military populations among 1752 documented cases

Study population	No. of confirmed cases[a]/no. patients tested <15 years	≥15 years	Significance (*P* value)	All ages
Civilian				
Males	167/347 (48·1%)	163/434 (37·1%)	<0·001	330/781 (42·2%)
Females	146/311 (46·9%)	92/374 (24·6%)	<0·001	238/685 (34·7%)
Total	313/658 (47·6%)	255/808 (31·6%)	<0·001	568/1466 (38·7%)
Military[b]				
Males	10/20 (50·0%)	86/179 (48·0%)	>0·3	96/199 (48·2%)
Females	8/15 (53·3%)	29/72 (40·3%)	>0·3	37/87 (42·5%)
Total	18/35 (51·4%)	115/251 (45·8%)	>0·3	133/286 (46·5%)

[a]Virologically and/or serologically confirmed.
[b]Including family members.

Table 5. Numbers and percentages of primary infections by age group in civilian and military populations from whom a positive diagnosis was obtained by virus isolation

Age group	No. primary infections/no. sera tested Civilian population	Military population[a]
<15 years	91/120 (75·8%)	10/12 (83·3%)
≥15 years	66/119 (55·5%)	67/78 (85·8%)
Total	157/239 (65·7%)	77/90 (85·5%)

[a]Including family members.

shown in Fig. 1.

The weekly distribution of declared cases according to their geographical location is shown in Fig. 2. Table 1 shows the incidence rates of declared cases by island group. Furthermore, amongst 6034 declared cases, 60·3% were <20 years old.

Overall, virological and/or serological positive results were obtained for 1966 of 4792 patients subjected to laboratory testing (41·1%). Confirmation was obtained by virus isolation for 1196 patients (24·9%) and by IgM capture ELISA (in first serum or paired sera) for 770 patients (16·1%). Dengue 1 was the main serotype isolated since December 1988, May 1988 being the last time dengue 4 was recovered. However, between mid-April 1989 and late June 1989, 5 cases of dengue type 3 were identified. Preliminary data on the dengue 3 epidemic which was later recognized in September 1989 have been reported elsewhere (CHUNGUE *et al.*, 1990).

Table 2 shows the results of the 2 methods of estimating the attack rate during the epidemic. Thus, the combined results of IgM and IgG prevalence showed an attack rate of 44% at week 17 in the cohort of soldiers. Of 11 subjects who became positive for IgM and/or IgG antibody, 7 reported a febrile syndrome during the study period. The attack rate was at least 41·1%, estimated by calculating the difference between the serological prevalence rate obtained in a random sample of susceptible children bled at the end of the epidemic (week 17) and that obtained in a similar sample before the epidemic.

Dengue virus was isolated from 3 of 59 pools of *Ae. aegypti* collected in sentinel stations (663 mosquitoes), and from none of 21 pools of *Ae. polynesiensis* collected in the same areas (92 mosquitoes). In addition, all 4 pools of *Ae. aegypti* (74 mosquitoes) collected around the house of a confirmed case were positive. All isolates were dengue type 1 viruses.

Study of 1752 documented cases

Dengue was confirmed virologically and/or serologically in 701 documented cases (40%). The frequency of the various symptoms observed in these confirmed cases is presented in Table 3. Analysis of questionnaires showed that 75·9% of the patients consulted their physician before day 4 of illness. No case fullfilling the World Health Organization criteria for dengue haemorrhagic fever/dengue shock syndrome was reported.

The distribution of documented cases by sex did not differ according to the age groups in either civilian or military populations ($P>0·05$, Table 4). Table 4 shows the age and sex distribution of the confirmed cases in both populations. Table 5 shows that 75·8% of civilian children <15 years old and 85·5% of the total military population were primary infections.

The percentage of cases confirmed by virus isolation or detection of anti-dengue IgM antibodies among 701 confirmed cases according to day of illness is shown in Fig. 3. Of 522 laboratory confirmations in patients who had blood taken before day 5 of illness, 90·6% were obtained by virus isolation, 8·2% by IgM detection, and 11% by both methods. Conversely, on or after day 5 of illness, 19·5% were obtained by virus isolation, 77·1% by IgM detection and 3·3% by both methods.

Total leucocyte and platelet counts were obtained for 280 confirmed cases. Leucopenia (total leucocytes $<4\times10^9$/litre) was recorded in 62·5% of the confirmed cases (≥15 years). Thrombocytopenia ($<150\times10^9$/litre) was observed in 27·2% of the confirmed cases.

Discussion

Surveillance of the epidemic

Dengue has occurred in French Polynesia as successive epidemics, especially between 1969 and 1979, with each epidemic involving a different serotype. Each time, the epidemic serotype replaced the unique endemic serotype that had been transmitted during the preceding inter-epidemic period. The reappearance of dengue 1 in late 1988 occurred while the endemic transmission of dengue 4 was very low. Although control efforts were initiated within a few days after its recognition, the epidemic developed explosively, according to all the indicators shown in Fig. 1.

Fig. 2 shows that the epidemic moved from the Windward Islands to the Leeward Islands and on to the Marquesas and Austral Islands. This observation is consistent with the fact that population movement by air is more intense between Tahiti and Leeward Island than between Tahiti and Marquesas or Austral Islands. Furthermore, the incidence rate of sentinel cases was higher in these remote islands (Table 1). At present, we cannot draw any conclusions from these results since (i) they might be due to varying degrees of survey coverage of the different populations, and (ii) bias in data collection certainly occurred: patient motivation for presentation, and the interpretation of case definition by sentinel physicians and their own enthusiasm for reporting, differed in different areas.

The age distribution of reported clinically suspect cases agreed with the preceding epidemiological background that suggested higher susceptibility in children (CHUNGUE *et al.*, 1989b). Moreover, if the serological attack rates (41·1%–44%) were applied to an estimated susceptible population of 45 000, the total serologically confirmed case incidence in the Windward Islands would be 18 495–18 980. Although declining thereafter, dengue 1 transmission continued until November 1990

at a lower level (CHUNGUE *et al.*, 1990). Since French Polynesia had experienced 2 extensive dengue 1 epidemics in the past (ROSEN, 1958; KAUEFFER *et al.*, 1976), the proportion of the population infected with dengue 1 in late 1990 would be around 70%. Thus, the decline of epidemic transmission may be related to the increasing level of immunological coverage of the general population. Although community-based vector control has been maintained constantly, the impact of control efforts on the course of the epidemic is difficult to evaluate and will be discussed elsewhere (P. Barbazan, personal observations). Nevertheless, virus isolation from mosquitoes provided evidence that dengue 1 was transmitted by *Ae. aegypti*, which is widely distributed in French Polynesia.

Study of documented cases

The proportion of confirmed cases was higher in both civilians <15 years old (46·5%) and in the overall military population (47·5%) when compared to that observed in civilians ≥15 years old (31·1%, $P<0·05$). These results confirmed the susceptibility to dengue infection of children born after the previous dengue 1 epidemic (KAUEFFER *et al.*, 1976) and individuals living in French Polynesia on a temporary basis. Moreover, primary infections were predominant in children <15 years old and in the total military population (Table 5).

The proportion of confirmed cases among patients aged 15 years or more was higher in male civilians (Table 4; $P<0·001$). That difference was not observed in the military population. We have not, so far, an adequate explanation for these observations. Work habits causing male civilians to be more exposed to mosquitoes might be related to the higher infection rate. Some authors have reported a predominance of men among dengue sufferers (LE GONIDEC *et al.*, 1982; CHAN *et al.*, 1977; GUARD *et al.*, 1984), while others have reported a higher frequency in females (GUZMAN *et al.*, 1984). These discrepancies may have arisen because the population studied was not fully representative of the total susceptible population.

Most of the patients consulted a physician during the febrile phase and had blood taken for laboratory confirmation at that time. This observation emphasizes the importance of early diagnosis. Before day 5 of illness, the diagnosis was mostly confirmed by virus isolation. Conversely, on or after day 5 it was usually confirmed by the detection of IgM (Fig. 3). The overall confirmation rate was probably underestimated, as paired sera were not available for most of the cases and definitive confirmation could not be made, especially for those who had blood taken at day 4 or 5 of illness. Indeed, a higher isolation rate might be expected if serum samples had been used at a lower dilution. However, a 1:40 dilution rather than 1:10 was preferred because of toxicity to mosquito cells (unpublished observations). Also, a higher confirmation rate would be obtained if the cut-off titre for a positive result in the IgM capture ELISA were set at a reciprocal titre of 100 instead of 400. Nevertheless, our results confirmed that virological and serological confirmatory methods are complementary in the light of the clinical history of patients; also leucopenia and thrombocytopenia were confirmed as good predictors of dengue diagnosis. The symptoms were typical of classical dengue fever in the majority of cases. Only minor haemorrhagic manifestations were observed.

The study of this epidemic indicated many of the difficulties in interpreting data collected by different means. Biases occurred in each system of surveillance and compliance of clinicians is difficult to maintain during a long period of time. Data may be influenced by incorrect initial diagnosis of other concurrently circulating viral diseases, and clinically-based surveillance may result in over estimation (DIETZ *et al.*, 1990). However, in our attempt to describe the epidemiological pattern and to monitor the surveillance of the epidemic, satisfactory results concerning time, age and geographical distributions were obtained. The weekly number of requests submitted for laboratory confirmation of diagnosis together with the level of the confirmation rate appeared to be a good alternative for estimating case distribution time trends. Finally, this study emphasized the need for lab-oratory-based dengue surveillance systems to measure the real incidence of the disease.

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