Research/Recherche

Dengue type 1 epidemic with haemorrhagic manifestations in Fiji, 1989–90

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A dengue type 1 epidemic occurred in Fiji between July 1989 and July 1990. Virus isolations in C6/36 cell cultures and Toxorhynchites *mosquitos yielded 36 strains. Of the 3686 cases recorded by the Ministry of Health, 60% involved indigenous Fijians and 37%, Indians. A house-to-house survey revealed that a large majority of patients had classical dengue symptoms and 8% reported haemorrhagic manifestations. Among the children and adults hospitalized for dengue, 43% had haemorrhagic manifestations, including epistaxis, gingival bleeding, haematemesis, melaena and haematuria. A total of 15 patients with haemorrhagic manifestations and/or shock died, 10 of whom were aged 0–15 years; the diagnoses were confirmed in four cases by virus isolation or serology.*

Introduction

Over the last two decades, dengue virus infections have become a major cause of morbidity and mortality in the Pacific region. In Fiji, two major epidemics caused by dengue types 1 and 2 occurred in the period 1971–75. The dengue type 2 epidemic in 1971 (3400 reported cases) occurred after a quiescent period of about 25 years, and most patients presented with classical dengue symptoms; no cases of dengue haemorrhagic fever (DHF) were recorded (*1*). The epidemic of dengue type 1 in 1975 was more severe: there were cases of haemorrhagic disease and several deaths occurred (*2, 3*). Between 1975 and 1989 there was no major epidemic, although localized outbreaks and sporadic cases occurred.

In July 1989, cases of dengue-like illness appeared in hospitals and health centres in Suva, the capital, and by September an outbreak of dengue fever caused by type 1 virus occurred in other parts of Fiji. The results of the clinical, virological, and epidemiological investigations into this epidemic are presented below.

Materials and methods

Outbreak area

Fiji consists of two large islands, Viti Levu and Vanua Levu, and many small ones (Fig. 1). The total population of 750 000 comprises 49% ethnic Fijians, 45% Indians, and 6% other racial groups. Suva lies on the south-east coast of Viti Levu and has a population of about 150 000.

Fig. 1. **Map showing the main islands of Fiji.**

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Survey of cases

Notifications of dengue and dengue-like illness in the Medical Records Department of the Ministry of Health were reviewed, as were records of cases admitted to paediatric and medical wards of the Colonial War Memorial Hospital. Data on cases of dengue in Fiji since 1971, including information obtained both from the Ministry of Health and the Wellcome Virus Laboratory, Suva, are given in Table 1.

In order to determine the relationship between the true case incidence and the reported incidence, we carried out a house-to-house survey in Suva and its environs during March and April 1990, covering 81 households and 426 people, of whom 257 (60%) were Fijians, 131 (31%) were Indians and 38 (9%) belonged to other ethnic groups. The houses were selected at random and questionnaires were administered seeking information about the occurrence of dengue-like illness in the occupants. After July 1989, when the epidemic was confirmed, persons were considered to have had dengue or dengue-like illness if they had experienced fever lasting more than 3 days accompanied by one or more of the following symptoms: headache, joint pains, muscle pains, rash, epigastric discomfort, and bleeding. The data obtained were analysed using χ^2 tests.

Table 1: **Dengue and dengue-like illnesses in Fiji, 1971–90**

	No. of cases	No. of cases of DHF[a]	No. of deaths	Virus type
1971	2 960	0	0	dengue 2
1972	446	0	0	dengue 2
1973	132	0	0	
1974	25	0	12	dengue 1
1975	16 203	Many	0	
1976	10	0	0	
1977	1	0	0	
1978	3	0	0	
1979	4	0	0	
1980	127	0	0	
1981	18	Few	1	dengue 4[b]
1982	676	0	0	dengue 2[b]
1983	238	0	0	dengue[c]
1984	190	0	0	
1985	31	0	0	dengue[c]
1986	269	0	0	
1987	432	0	0	
1988	22	0	0	
1989–90	3 686	15	15	dengue 1

[a] DHF = dengue haemorrhagic fever.
[b] Confirmed by serology only.
[c] Serotype not determined.

Virus isolation and identification

Blood samples collected from acute cases were centrifuged at 1500 rpm and stored at –60 °C or –20 °C until tested. Tissue culture or mosquito inoculation was used in attempts to isolate the virus.

Virus isolation in mosquitos involved intrathoracic inoculation of *Toxorhynchites* spp. with undiluted serum (*4*). After extrinsic incubation for 14 days, head squashes of inoculated mosquitos were examined for dengue virus antigen by the direct immunofluorescent antibody test using an FITC conjugate prepared from pooled high-titre (>5120) human serum (*5*).

Specimens tested in tissue culture were inoculated into C6/36 (*Aedes albopictus*) cell cultures seeded at 3×10^5 cells per ml in 25-ml plastic bottles (*5*). Undiluted serum (0.1 ml per bottle) was inoculated into duplicate bottles and incubated at 34 °C for 7 days. Infected cultures were harvested and assayed for dengue virus antigen by the indirect fluorescent antibody and complement fixation tests.

Serology

Serum samples were tested for immunoglobulin M (IgM) by a capture enzyme-linked immunosorbent assay (ELISA) at the Dengue Branch, Division of Vector-Borne Infectious Diseases, San Juan, Puerto Rico, as described previously for Japanese encephalitis (*6*), and modified for dengue (*7*). Immulon II flat-bottomed microtitration plates were coated with goat anti-human IgM antibody diluted in carbonate–bicarbonate buffer (pH 9.2). The plates were washed, blocked with 4% bovine serum albumin, and washed again; the test serum was added at a dilution of 1:40. After incubation for 2 hours at room temperature and another washing, 16 haemagglutinating (HA) units of mouse brain or tissue culture antigen containing normal human serum extracted with 20% acetone was added. The plates were incubated overnight at 4 °C and washed again. Anti-dengue horseradish conjugate that had been diluted in phosphate-buffered saline containing normal human serum extracted with 20% acetone was added and the plates were incubated for 1 hour at 37 °C. The plates were then washed again, 2,2'-azinobis(3-ethylbenzothiazoline-6-sulfonate) substrate was added, and after incubation for 2 hours the plates were read at λ = 410 nm using a Dynatech Minireader II. Serum samples with absorbances ≥0.20 were taken as positive.

Indirect immunofluorescent staining of head squashes and C6/36 cell culture harvests was per-

formed by standard procedures, using serotype-specific dengue monoclonal antibodies obtained from the Centers for Disease Control, Fort Collins, CO, USA (*5*).

Complement fixation tests were performed with tissue culture harvests using the method described by Weinbren (*8*), adapted to microtitration plates. Infected tissue culture fluids were tested against a 1:8 dilution of a known dengue 1 positive serum.

Haemagglutination inhibition (HI) tests were performed on paired serum samples using the method described by Clarke & Casals (*9*), adapted to microtitration plates. Kaolin-treated sera were tested for endpoints against 4–8 HA units of dengue antigens prepared by tissue culture and extracted with sucrose acetone. Paired sera were tested in twofold dilutions in the same test; patients with a fourfold or greater rise in antibody titres were taken to be positive for dengue. Patients were classified on the basis of serological response as having had primary or secondary infections, using the criteria proposed by Reed at al. (*2*) with minor modifications. Primary infection was considered to be present if convalescent serum, obtained after 10–14 days, had an antibody titre of ≤1:640 and if acute serum, collected <5 days after their illness began, had a titre <1:10. Patients with HI antibody titres ≥1:1280 in convalescent sera and ≥1:10 in acute sera were regarded as having secondary infections. Those with a positive IgM and/or a secondary type HI response in either serum specimen were designated presumptive dengue cases.

The plaque reduction neutralization test (PRNT) was performed in LLC–MK2 cell culture on serum samples from suspected dengue patients as previously described (*10*). Twofold dilutions of serum specimens were heat-inactivated at 56 °C for 30 minutes and inoculated on to LLC–MK2 cell monolayers in 12-well tissue-culture plates. After the plates had been incubated for 1 hour at room temperature, 1 ml of overlay medium containing 1% purified agar was added to each well. The plates were then incubated at 36 °C for 6 days under an atmosphere containing 5% carbon dioxide. The reciprocal of the serum dilution that produced >50% plaque count reduction compared with a normal human serum control was used as the PRNT titre.

Results

After diagnosis of the first cases of dengue fever during routine serology, reports from outpatient clinics at the Colonial War Memorial Hospital and from private clinics indicated that many patients were presenting with dengue-like illness. However, notifications were not received by the Ministry of Health until September 1989, and these were largely from Suva. Reports of dengue cases from other parts of the country began to appear in October, and the epidemic peaked in November 1989 (Fig. 2). Of the 3686 cases notified by the end of July 1990, 55% were males and 45% were females; 60% were Fijians, 37% were Indians, and 3% belonged to other racial groups.

The house-to-house survey indicated that 182 (43%) of the interviewees had a history of clinical dengue over the previous 6 months (Table 2). A slightly higher incidence of dengue cases was observed among the age groups 0–9 years and 10–19 years, although the differences were not statistically significant.

The incidence was 44% in Fijians, 39% in Indians, and 45% in the other ethnic groups; in contrast, 63% of the persons reporting dengue-like illness were Fijians, 28% were Indians, and 9% belonged to other ethnic groups. A history of haemorrhagic manifestations was reported by 15 (8%) of the interviewees, of whom 6 and 5, respectively, were aged 0–9 years and 10–19 years. Haemorrhagic manifestations were reported by two, zero, and two persons, respectively, for the age groups 20–29 years, 30–39 years, and ≥40 years. Of the 15 cases with haemorrhagic manifestations, 13 were Fijians, one was Indian, and one was European. Seven patients reported a history of respiratory symptoms in addition to those of dengue. Epistaxis was the commonest haemorrhagic manifestation, affecting eight persons. Other haemorrhagic manifestations included gingival bleeding (2 persons), haematemesis (2), haematuria (3), and melaena (3).

Fig. 2. **Distribution of cases of dengue notified, by month, in Fiji, 1989–90.**

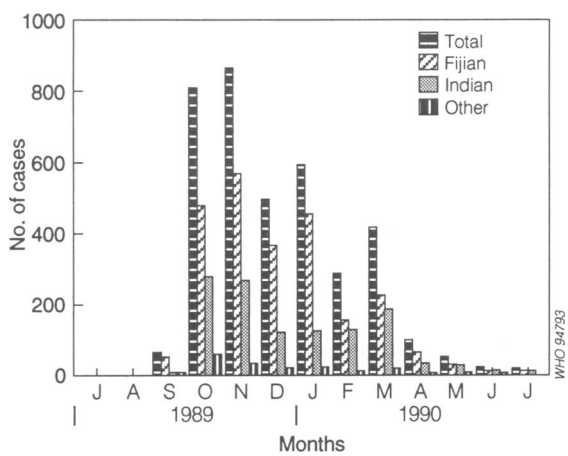

Table 2: **Results of the house-to-house survey of dengue cases, Suva, Fiji, 1990**

Age group (years)	Total (all races): n^a	Total (all races): No. of cases	Fijians: n^a	Fijians: No. of cases	Indians: n^a	Indians: No. of cases	Others: n^a	Others: No. of cases
0–9	80	41 (51)[b]	46	25 (54)	23	10 (43)	11	6 (55)
10–19	98	60 (61)	66	43 (65)	26	13 (50)	6	4 (67)
20–39	146	48 (33)	80	26 (33)	50	16 (32)	16	6 (38)
≥40	102	33 (32)	65	20 (31)	32	12 (38)	5	1 (20)
All ages	426	182 (43)	257	114 (44)	131	51 (39)	38	17 (45)

[a] No. of residents surveyed.
[b] Figures in parentheses are percentages.

Clinical features of hospitalized patients

A wide spectrum of clinical manifestations was observed during the epidemic, ranging from mild, nondescript febrile illness to severe haemorrhagic disease and shock. Of the persons seen at outpatient clinics, 90% had classical dengue symptoms characterized by fever, headache, myalgia, arthralgia and retro-orbital pain. Maculopapular rash and vomiting occurred in a few patients.

There were both children and adults among the patients who required hospitalization. Of 202 children admitted to the paediatric ward, 43% had one or more haemorrhagic manifestations, and 13% developed shock. Autopsies were performed on 6 of the 15 fatal cases, and haemorrhages of the stomach and lungs occurred in most of these patients. Haemorrhages or congestion and oedema were found in the spleen, pancreas, or brain of two others. The clinical details for two hospitalized paediatric patients are given below.

Clinical histories of two paediatric patients. The first patient, an 11-year-old Fijian male, was admitted with a history of 2 days of fever, epigastric pain, and one episode each of melaena and haematemesis followed by convulsions. Before admission, the patient had taken a concoction of herbs and other unknown substances to relieve the fever. A provisional diagnosis of peptic ulcer or DHF was made. On clinical examination the patient was febrile and had a blood pressure of 80/60 mmHg (10.7/8.0 kPa) and a pulse rate of 120 per minute. He was pale and lethargic but there was no neurological deficit; also, there was bleeding from the anus.

On the second day after admission the patient had three episodes of bloody stools. Haematological studies revealed the following values: haemoglobin, 5.6 g per 100 ml; total leukocyte count, 4200 per µl; haematocrit, 20%; platelet count, 36 000 per µl. The patient received a transfusion of five units of blood.

A laparotomy was performed in order to determine the cause of the gastrointestinal bleeding. No gross lesions of the gut were found but there was blood in the terminal ileum, caecum, and large bowel. The patient continued to pass bloody stools and 200 ml of blood was aspirated from the stomach. Because of the continued bleeding, 300 ml of platelet-rich plasma was transfused on the fourth day after admission. Later on the same day the bleeding stopped and the patient's condition improved.

Acute and convalescent serum samples collected on the third and seventeenth days of illness had dengue HI antibody titres of 1:320 and 1:1280, respectively.

The second patient, a 12-year-old Indian male, was admitted with a history of fever, bloody stools and haematemesis. He had an enlarged posterior cervical lymph node, a feeble pulse of 120 per min, tachycardia and a blood pressure of 85/50 mmHg (11.3/6.7 kPa). The haematemesis and melaena continued, and on the third day after admission he was transfused with two units of blood, following which his blood pressure increased to 130/90 mmHg (17.3/12.0 kPa). The results of haematological investigations were as follows: haemoglobin, 17.1 g/100 ml; packed cell volume, 53%; total leukocyte count, 16 100 per µl; platelet count, 44 000 per µl.

The patient became comatose on the fourth day after admission but improved on receiving 300 ml of 10% mannitol solution. Examination of the lungs on the fifth day revealed crepitation and opacity of the anterior and posterior areas. From the seventh day onwards the patient exhibited pupillary dilatation, cerebral oedema, hypoxia, and spasticity of the limbs. The bleeding episodes continued until the eleventh day, when the patient died. No virus was isolated from samples of acute-phase blood, but both the acute and convalescent sera were positive for dengue IgM antibody. HI antibody titres in acute and convalescent serum samples were 1:320 and 1:2560, respectively.

In the adult wards, 200 patients were hospitalized because of DHF; 126 (63%) were ethnic Fijians, 60 (30%) were Indians, and 14 (7%) belonged to

other races. Clinical manifestations were similar to those described for paediatric patients.

Of the 15 persons whose deaths were attributed to dengue virus infection, 10 were aged 0–15 years and five were older children and adults; four of the cases were confirmed by virus isolation or serology.[a]

Virological and serological studies

A total of 36 strains of dengue 1 virus were isolated, 17 in tissue culture and 19 by mosquito inoculation.

Of 269 paired serum samples examined for dengue IgM antibody, 148 (55%) were positive; 64 (41%) had IgM antibody in both acute and convalescent specimens, and 84 (59%) only in the latter. Of 85 single specimens, 45 (53%) were positive. Of 123 serum samples positive for dengue virus HI antibody, 75 had classifiable serological responses, 41 (55%) of which were primary infections and 34 (45%), secondary. Both clinical and serological data were available for only 36 patients; 13 (36%) had primary infections and 23 (64%), secondary. Two of 13 patients with primary antibody responses and 14 of the 23 with secondary responses had severe haemorrhagic disease.

The PRNT results for acute and convalescent serum samples from 10 patients with primary HI responses showed that all of them had their highest neutralization indices against dengue type 1 virus; this supported the virological results, indicating a single-serotype epidemic.

Discussion

Dengue has emerged as a leading cause of morbidity in the South Pacific region; since 1971, epidemics caused by all four serotypes have occurred repeatedly in several Pacific island countries. In Fiji there has been clinical evidence of dengue each year for the past 20 years; however, only two large epidemics have previously been documented.

Of the 3686 cases of clinical dengue that were officially reported for the 1989–90 outbreak, the incidence was higher among Fijians than Indians, whereas during the 1975 type 1 epidemic the incidence was higher among Indians (*2*). The results of our house-to-house survey were consistent with official notifications and supported the hospital data, indicating that there were more cases among Fijians than other racial groups. More cases were reported for children than adults, presumably because the adult population had been exposed to dengue type 1 in 1975.

The dengue epidemic in 1989–90 was one of the most severe experienced in Fiji; there were many cases of haemorrhagic disease and a record number of deaths. Severe haemorrhagic disease occurred among a higher proportion of ethnic Fijians (63%) than Indians and other racial groups, but this was probably because of the greater number of Fijians with dengue who presented at hospitals.

A total of 15 suspected dengue-related deaths were recorded during the epidemic. In addition there were anecdotal reports of several deaths attributable to dengue in various parts of the country. Although more cases of DHF were reported among Fijians, 9 of the 12 deaths associated with dengue involved Indians. It is not clear whether this was due to a racial difference in susceptibility or to an underrecording of deaths among Fijians; however, no mortality differences between races were observed by Reed et al. during the 1975 Fijian dengue epidemic (*2*).

The two large outbreaks of DHF reported in Fiji have been associated with the type 1 virus. The 1975 outbreak, estimated to have resulted in 1600–2400 DHF cases (*2*), was preceded by a type 2 epidemic. The 1989–90 outbreak was preceded by four sporadic outbreaks, two of them caused by dengue types 2 and 4 (Table 1).

It is noteworthy that no cases of DHF and associated deaths were officially documented during the 1971–72 dengue 2 outbreak, when the prevalence of pre-epidemic heterologous dengue virus antibody in Fiji was very low (*1*). Haemorrhagic dengue occurred only after at least two dengue serotypes had been introduced into the population (Table 1). Although the mechanism of pathogenesis of DHF remains unclear, several factors contribute to its development, including antibody-dependent enhancement of dengue virus replication in the mononuclear cells of individuals previously infected by another serotype variation of dengue virus (*11, 12*), and unidentified epidemiological and host risk factors (*12*). A total of 14 out of 15 patients with severe haemorrhagic disease had antibody responses compatible with secondary infection, despite the occurrence of more primary dengue cases during the outbreak. However, the epidemiological and laboratory data are insufficient to permit evaluation of the roles of any of these factors in the pathogenesis of DHF.

Although only dengue type 1 and type 2 viruses have been isolated in Fiji, all four dengue virus serotypes are present in the Pacific region (*13*). The continued circulation of these serotypes in the region holds serious public health implications for Fiji. More epidemics can be expected, especially if dengue 3 virus is introduced into the country. It is there-

[a] The clinical, laboratory and post-mortem findings for 12 of the suspected dengue patients with a fatal outcome are available upon request.

fore necessary to improve surveillance and vector control efforts. Morbidity and mortality caused by dengue are grossly underreported; it will only be possible to assess in full the impact of outbreaks on the general population and the health services if there is accurate reporting of cases and of deaths associated with the disease.

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Résumé

Epidémie de dengue de type 1 avec manifestations hémorragiques à Fidji, 1989–1990

Une épidémie de dengue avec manifestations hémorragiques s'est déclarée à Fidji entre juillet 1989 et juillet 1990. Nous avons passé en revue les notifications officielles de cas de dengue et de maladie évoquant la dengue faites auprès du Ministère de la Santé à Suva, et réalisé une enquête de porte en porte. Le Ministère de la Santé a enregistré 3686 cas pendant la durée de l'épidémie, dont 60% concernaient des Fidjiens indigènes, 37% des Indiens et 3% d'autres ethnies. L'enquête de porte en porte a également montré un plus grand nombre de cas chez les Fidjiens que parmi les autres groupes raciaux.

Les examens de laboratoire ont montré que l'épidémie était provoquée par le virus de la dengue type 1. Les isolements de virus réalisés en culture de cellules C6/36 et chez des moustiques *Toxorhynchites* ont donné 36 souches. Des épreuves sérologiques ont été réalisées sur des prélèvements de sérums de cas suspects, par épreuve immuno-enzymatique (ELISA) avec capture d'IgM, inhibition de l'hémagglutination (HI) et neutralisation (réduction des plages). On a obtenu des résultats positifs pour les IgM antidengue sur 148 sérums appariés et 85 sérums uniques. Les réponses en anticorps mesurés par HI chez 75 malades ont montré qu'il s'agissait dans 55% des cas de primo-infections et dans 45% des cas, d'infections secondaires. Les résultats des épreuves de neutralisation par réduction des plages sur des sérums aigus et de convalescence prélevés sur dix malades ayant une réponse HI primaire correspondaient avec ceux de l'analyse virologique.

Les manifestations cliniques observées pendant l'épidémie étaient variées, allant d'une affection fébrile bénigne à une maladie hémorragique sévère et au choc. Parmi les malades vus dans les dispensaires, 90% présentaient les symptômes classiques de la dengue, avec fièvre, céphalées, myalgies, arthralgies, douleurs rétro-orbitaires, éruptions maculopapuleuses et vomissements; 10% présentaient des manifestations hémorragiques. Parmi les enfants et les adultes hospitalisés pour dengue, 43% présentaient des manifestations hémorragiques, avec épistaxis, hémorragies gingivales, hématémèse, méléna et hématurie. Quinze malades présentant des manifestations hémorragiques et/ou un choc sont décédés, dont 10 âgés de 0 à 15 ans. Dans quatre de ces cas mortels, le diagnostic avait été confirmé par isolement du virus ou sérologie.

La dengue a fait son apparition en tant que cause majeure de morbidité dans la région du Sud du Pacifique. Depuis 1971, des épidémies de dengue dues aux quatre sérotypes se sont répétées dans plusieurs îles du Pacifique. L'épidémie décrite ici a été l'une des plus graves enregistrées à Fidji, par sa morbidité et sa mortalité. La maladie a provoqué de nombreux cas hémorragiques, et un nombre de décès sans précédent. La circulation des virus de la dengue dans la région constitue une menace sérieuse pour la santé publique dans les petits pays insulaires du Sud-Ouest du Pacifique. On s'attend à ce que d'autres épidémies frappent Fidji, surtout si le virus de la dengue type 3 est introduit dans le pays. Il est donc nécessaire de renforcer les activités de surveillance et les efforts de lutte antivectorielle.

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