

The 1993 dengue 2 epidemic in Charters Towers, North Queensland: clinical features and public health impact

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SUMMARY

In 1993 an epidemic caused by dengue virus type 2 occurred in several North Queensland population centres. Charters Towers, estimated population 10000, had 155 officially notified cases. An analysis of symptoms was undertaken using a random sample of 1000 residents to determine specificity of symptoms, the subclinical infection rate, and to establish the true extent of the epidemic. Retrospective diagnoses of dengue fever were based on the presence of both serum dengue 2 neutralizing antibody and presence of symptoms. An estimated 20% of the population had dengue fever. The rate of subclinical infections in this epidemic was 14.6%. There were no symptoms that were specific for dengue fever. Bleeding occurred more frequently in people who recalled a previous dengue infection during a dengue 1 epidemic 12 years earlier (55.6% vs. 16.8%, $P = 0.003$). Surveillance for future epidemics should be based on serological and virological confirmation of dengue virus infection amongst symptomatic patient.

INTRODUCTION

Classical dengue fever is caused by one of the four serotypes of dengue virus. The virus is transmitted from human to human by the peridomestic mosquito *Aedes aegypti*. The illness is characterized by the sudden onset of fever, headache, aching back and limbs, rash and occasionally, minor bleeding. A more severe form of dengue infection, dengue haemorrhagic fever (DHF), is increasingly being recognized and is associated with sequential infections with different dengue serotypes [1]. The proportion of individuals infected with a dengue virus that develop symptoms has been variously estimated at 13–100% [2–6].

During 1992–3 there was an epidemic of dengue 2 that affected several population centres in the Northern Tropical area of Queensland, Australia. The Charters Towers community, estimated population 10000 was affected over a 4-month period from

March–June in 1993. There were 155 laboratory confirmed cases and a further 495 cases notified on clinical grounds [7]. There had been epidemics of dengue fever in 1981 (dengue 1) [8], 1954 (dengue 3) [9], and 1941–3 (dengue 2) [10]. Epidemics dating from as early as the 1870s are recorded [11].

In 1995 a cross sectional survey of 1000 residents of Charters Towers was conducted. The aims were to determine the specificity of dengue symptoms and to calculate the proportion of symptomatic patients. We also sought to determine the impact of the epidemic and to what extent it was underestimated by the official notifications of illness.

MATERIALS AND METHODS

Research design

A random sample of 1000 people living in Charters Towers (latitude 20° 5' S, longitude 146° 16' E) was enrolled by dialling every tenth number in the local telephone directory. Where possible, all eligible

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persons in the same household were enrolled. People > 14 years of age who had been living in Charters Towers during the epidemic and were resident in North Queensland in 1981 were eligible for inclusion. This latter requirement was included to examine whether the clinical features of dengue 2 infection were influenced by having had a dengue 1 infection during an epidemic which occurred in 1981. Written consent was obtained. A questionnaire was administered by one single investigator and a blood specimen was obtained.

In the questionnaire participants were asked to recall whether they had been unwell during the period of the dengue epidemic. The recollection of retro-orbital pain, backache, headache, bleeding, rash, joint pain, bone pain, itch, diarrhoea, vomiting, stomach ache, cough, sore throat, lethargy, swollen glands, perversion of taste and skin sensitivity was specifically sought. Participants were asked how long they had been unable to work, whether they consulted a doctor, or were hospitalized. The opinion of their doctor at the time (as recalled by the participant), prior history of dengue, and travel to tropical regions outside of Australia were recorded.

Serological tests

All sera were tested using the haemagglutination-inhibition (HI) assay of Clarke & Cassals [12] and a commercial ELISA for IgG antibody (Panbio, Brisbane, Australia). Samples positive in either of these screening tests were further analyzed using a dengue 2 plaque reduction neutralization test (PRNT) [13]. The HI test is sensitive and detects antibody up to 50 years after infection whilst the PRNT detects serotype specific antibody [14].

Statistical analysis

All questionnaire data and laboratory results were entered into the database and statistical package 'Intercooled STATA 4.0 for Windows'. χ^2 tests, *t* tests, and logistic regressions were performed using this program.

RESULTS

Of the 1000 people interviewed all but one provided a serum specimen. There were 367 males and 633 females. The mean age was 48.8 (range 14–88) years. Antibodies to dengue, or the closely related flaviviruses, were detected in the serum of 619 people; 399

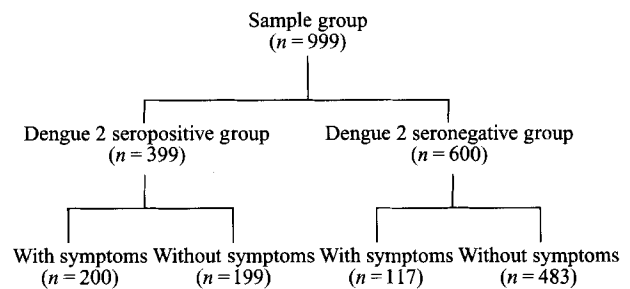


Fig. 1. Distribution of study subjects according to dengue 2 antibody status and their recollection of symptoms, Charters Towers, 1993.

(64%) of these sera had neutralizing antibody against dengue 2.

Illness was recalled by 200 people whose serum had dengue 2 neutralizing antibody. An additional 117 people without dengue 2 neutralizing antibody could recall an illness (Fig. 1). The proportion of males and females who could recall an illness was similar, 32.4% and 31.3% respectively ($P = 0.7$). Illness, in conjunction with dengue 2 neutralizing antibodies in serum, was recorded for 72 (19.6%) and 128 (20.2%) respectively ($P = 0.8$).

Only 23 people could recall having dengue fever in 1981, 9 had symptoms and serological evidence of dengue 2 infection in 1993 and 5 (55.6%) of these could recall bleeding symptoms during this epidemic. Their ages were 38–71 years and the bleeding sites included nose, gums, skin and gastrointestinal tract. There were 191 patients who had evidence of recent dengue 2 infection who could not recall having dengue in 1981, 32 of these people (16.8%) had bleeding ($P = 0.003$).

The rate of illness varied with age. Of the 538 people aged ≤ 50 years, representing a cohort of people born after the 1941–3 dengue 2 epidemic in North Queensland, 484 (90%) could recall symptoms of an illness during the epidemic if their serum contained dengue 2 neutralizing antibodies (Fig. 2). People > 50 years were less likely to have been unwell during the epidemic ($P < 0.001$). Symptoms occurred in 117 (19.5%) of dengue 2 seronegative people and did not vary significantly with age ($P = 0.27$) whereas symptoms occurred in 200 (50%) of patients who had dengue 2 antibodies and the rate decreased significantly with age ($P < 0.001$).

To calculate the symptomatic rate of dengue 2 infection, a person was assumed to have been infected during the most recent epidemic if their serum contained dengue 2 neutralizing antibody and they were born after 1943 (age ≤ 50). The background rate

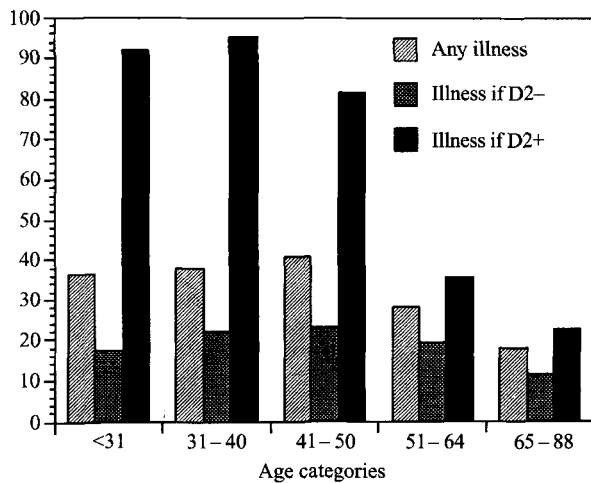


Fig. 2. Age specific rates of illness during the dengue 2 epidemic in Charters Towers, 1993. The rate of illness in the whole sample, and that found in people with and without dengue 2 neutralizing antibody in their serum (D2+ and D2- respectively) are shown.

Table 1. Comparison of the number of people aged 50 years or less with recollection of symptoms according to the presence or absence of dengue 2 neutralizing antibody (D2+ve and D2-ve respectively) in their serum, Charters Towers, 1993

	Den2+ve	Den2-ve
Symptoms	123	84
No symptoms	16	315
Total	139	399
Symptoms in people with dengue 2 antibodies	Odds ratio 28.8 Attributable fraction 96.5%	

of illness in participants without dengue 2 neutralizing antibody in their serum was taken into account. There were 538 people in this group including 139 people who were dengue 2 seropositive. The odds ratio for illness in dengue 2 seropositive people was 28.8 and the attributable fraction of illness actually due to dengue 2 was 96%. It was calculated, therefore, that 85.4% of people aged 50 or less who were infected with dengue 2 had symptoms attributable to this infection (Table 1). Of the 16 people aged \leq 50 years who were dengue 2 seropositive but could not recall any illness, one had a prior history of dengue fever and three had travelled to dengue endemic areas. Had these people acquired immunity to dengue 2 prior to 1993 the symptomatic rate would be even higher.

An analysis of symptoms was conducted for people who recalled illness and whose serum contained

Table 2. Percentage frequency of various symptoms during a 1993 Charters Towers epidemic of dengue 2. Two groups of symptomatic patients, those with (D2 POS) and without (D2 NEG) serum dengue 2 neutralizing antibodies are compared

Symptom	Dengue 2 positive (n = 200) (%)	Dengue 2 negative (n = 117) (%)	P value
Fever	190 (95)*	100 (85.5)	0.003
Rash	111 (55.5)	23 (19.7)	< 0.001
Eye pain	138 (69)	58 (49.6)	0.001
Headache	186 (93)	97 (82.9)	0.005
Bleeding	37 (18.5)	5 (4.3)	< 0.001
Joint pain	177 (88.5)	86 (73.5)	0.001
Bone pain	136 (68)	48 (41)	< 0.001
Itch	88 (44)	28 (23.9)	< 0.001
Diarrhoea	43 (21.5)	23 (19.7)	0.697
Vomiting	81 (40.5)	32 (27.3)	0.018
Stomach ache	81 (40.5)	37 (31.6)	0.115
Cough	41 (20.5)	38 (32.5)	0.017†
Sore throat	56 (28)	40 (34.2)	0.247
Lethargy	191 (95.5)	102 (87.2)	0.007
Swollen glands	55 (27.5)	36 (30.8)	0.535
Taste change	134 (67)	33 (28.2)	< 0.001
Skin sensitivity	65 (32.5)	20 (17.1)	0.003

* Values in parentheses are percentages.

† Significantly more common in dengue 2 negative subjects.

dengue 2 neutralizing antibody. This was compared to the symptoms of seronegative individuals who were unwell during the epidemic (Table 2). Most symptoms were recorded more frequently in dengue 2 seropositive patients; only diarrhoea, stomach ache, sore throat and swollen glands occurred with a similar frequency in both groups. Bleeding, predominantly seen in the dengue 2 seropositive group, was reported mostly from the gums, nose and vagina (menstrual). One person had haematemesis and melaena. Cough was significantly more common in the dengue 2 seronegative group. Logistic regression analysis identified four symptoms: rash, bleeding, bone pain and taste alteration as being the symptoms most significantly associated with dengue 2 seropositivity. Using an algorithm which included the presence of one or more of these symptoms, 89% of the dengue 2 positive group and 58% of the dengue 2 negative group were identified. The positive predictive value for identifying people with serum dengue 2 neutralizing antibodies was 73%.

The average number of days lost through illness related to a dengue 2 seropositive illness was 10.5. Dengue 2 seronegative illness resulted in 8.2 days

being lost. The difference was significant in a two tailed *t* test ($P = 0.002$). Four people in each group claimed to have been incapacitated for over a month and were excluded from the analysis. One hundred and sixty-six of the symptomatic dengue 2 seropositive people visited their doctor (83%), compared with 68 (58%) of the dengue 2 seronegative group ($P < 0.001$). Of the dengue 2 seropositive group who visited their doctor 81% were told that they had dengue fever, 39% of the dengue 2 seronegative group were also informed that they had dengue fever ($P < 0.001$). Amongst symptomatic people with serum dengue 2 neutralizing antibodies 24 (12%) were hospitalized as were 4 (3.4%) of the dengue 2 seronegative group ($P = 0.009$).

DISCUSSION

The 1993 dengue 2 epidemic in Charters Towers infected an estimated 26% of the population who were previously unexposed to this virus [15]. The group in this study however had a higher mean age than the city as a whole and would have contained a higher proportion of immune individuals. Up to 40% of the people aged ≥ 51 were immune because of prior exposure to dengue 2. In our study group of 1000 people 200 (20%) had clinically apparent cases of dengue fever. Infection in the immunologically naive portion of the population caused illness in 85.4% of those infected. Had the whole population of 10000 been susceptible, there would have been 2600 infections and 2220 clinically apparent cases. It is estimated therefore, that between 2000 and 2220 cases of clinically apparent dengue occurred in the city. The lower estimate may be more realistic given the finding that children have more subclinical infections [16].

Based on the estimate of 2000 cases of dengue infection, the proportion of people presenting to their doctor and the proportion of those diagnosed clinically with dengue fever, it is calculated that 1345 people with dengue fever could potentially have been notified to public health authorities. At the same time 267 people might have been falsely reported as cases of dengue fever. The clinical diagnosis of dengue fever was correct for 81% of the participants. This is more sensitive than the clinical algorithm proposed in this study, or that used in a study conducted during a Brazilian epidemic [17]. The clinical diagnosis by the Charters Towers medical practitioners was also more specific. This suggests that clinical algorithms are unlikely to be more sensitive, or specific than the

conclusions based on the clinical judgements of medical practitioners, at least during an established epidemic.

Only 155 cases were officially reported to the National Notifiable Diseases Surveillance System, which requires serological or virological confirmation of infection. The reasons for the low notification rate were not fully investigated. Serological confirmation requires demonstration of IgM or a fourfold rise in IgG titre in paired serum samples. IgM detection in serum is a sensitive means of confirming a diagnosis of dengue fever, but only if serum is collected after the fifth day of illness when over 80% will be positive [14]. Some doctors ordered confirmatory testing for only one member of a sick family and were confident that others in the same household also had dengue fever. As doctors became accustomed to the disease they probably ordered less confirmatory testing. Some patients, aware that there was no treatment, did not visit their doctor. There is no doubt that other factors also contribute to the low notification rate and these probably vary between epidemics. The degree to which the true incidence of disease is underestimated by official notifications will also vary. There were 620 clinical notifications of disease and although this number is epidemiologically more meaningful it is also subject to variation depending on the enthusiasm of individual doctors in reporting suspected cases.

The finding of a low subclinical infection rate agrees with the findings of Halstead and colleagues [6] and Sharp and colleagues [5] who also made their observations using adult caucasian populations. In a Cuban study however, only 28% of the caucasian population who were dengue 2 seropositive could recall a 'dengue-like' illness during a dengue 2 epidemic 2 years previously and only 12% of the black population could recall being ill [4]. Two Puerto Rican studies also found a high subclinical infection rate [2, 3]. It is possible that viral subtypes may differ in frequency with which they cause clinically apparent illness. Racial and/or immunological factors, such as exposure to cross protective flaviviruses, might also explain the wide differences found in the clinical attack rates in these studies. A knowledge of the subclinical infection rate is important for the design of studies that seek to establish the proportion of a population at risk for secondary dengue infection and dengue haemorrhagic fever [18]. The results of the present study suggest that most adults in Charters Towers at risk for secondary infection will have had a previous clinical episode of dengue fever. In the event

of another dengue fever epidemic (caused by serotypes 1, 3 or 4) these people should be specifically targeted for advice concerning prevention of infection. The low subclinical infection rate found in this study also has implications for interepidemic surveillance. A surveillance system based on rapid confirmation of suspected dengue fever cases is currently practised in North Queensland and on the evidence presented here, appears to be justified. Where subclinical infection rates have been shown to be higher, serological surveillance of asymptomatic persons has been recommended [19].

The frequency of symptoms in those who were symptomatic and had dengue 2 antibodies was in general agreement with the frequency of symptoms reported in the Townsville epidemic the year previously although rash, reported in 71% and itch, reported in 58% of patients in Townsville [20], was reported more commonly than in the Charters Towers sample. The less frequent reporting of rash and itch was also found in an analysis of dengue fever patients reporting to the Charters Towers hospital [21] although symptoms which developed subsequent to the hospital attendance in that study would not have been recorded. Most of people in the present study had little difficulty in their recollection of symptoms despite 2 years having elapsed since the epidemic.

The incidence of bleeding was higher in patients who recalled having dengue fever in 1981, however the number of patients in this group was quite small. Based on the participants' recollections, the 1981 dengue 1 epidemic had a limited impact on the town. Although a diagnosis of DHF requires the documentation of thrombocytopenia and haemoconcentration in addition to bleeding [22], the finding suggests that an interval of 12 years between primary and secondary dengue infections is a risk factor for more severe dengue symptoms, including bleeding.

The female to male ratio of symptomatic, dengue 2 seropositive persons in this study was 1.05:1 ($P = 0.55$) which contrasts with ratios of 1.28:1 reported for the epidemic of dengue 2 reported in the neighbouring city of Townsville [20] and 1.6:1 found in patients who presented to the Charters Towers hospital during the epidemic [21]. This could be explained if females preferentially presented to their doctors, a finding that was not supported in this study, where 83.6% of females and 81.9% of males sought medical advice ($P = 0.76$). These other studies sampled relatively younger populations where men were more likely to spend their days away from the

family home and who may have had less exposure to infected mosquitoes.

The nature of the non-dengue illnesses suffered during the same period as the dengue epidemic remain poorly defined. There will always be a background of febrile illness in communities susceptible to dengue fever. Many of these illnesses will be due to cosmopolitan viruses but some may be the result of other mosquito-borne viruses. Some of the illnesses seen are clinically indistinguishable from dengue fever and are a cause for concern in interepidemic periods until dengue viral infection is excluded. Further investigation of these dengue like illnesses is needed to better understanding the epidemiology of arboviral infections in North Queensland.

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