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Clinical diagnostic delays and epidemiology of dengue fever during the 2002 outbreak in Colima, Mexico

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Abstract

Dengue fever is a re-emergent and challenging public health problem in the world. Here, we assess retrospectively the epidemiological and clinical characteristics of the 2002 dengue epidemic in the state of Colima, Mexico. This study is carried out by analysing a database containing demographic, epidemiological and clinical information. Of the 4040 clinical dengue cases diagnosed in the hospitals of the Mexican Institute of Public Health in the state of Colima, 548 cases were confirmed by laboratory tests, and 495 cases presented at least one haemorrhagic manifestation. Of the total clinically diagnosed cases, the most common symptoms observed were: fever (99.6%), headache (92.4%), myalgia (89.4%) and arthralgia (88.6%). The most common haemorrhagic manifestations were: petechiae (7.1%), gingivitis (3.4%) and epistaxis (3.6%). The median time between the onset of illness and visit to the health care clinic (diagnostic delay) was 1 day (interquartile range [IQR]: 0-3). For cases presenting haemorrhagic manifestations, the diagnostic delay was higher (median: 2 days, IQR: 0-4) than for non-haemorrhagic cases (median: 1 day, IQR: 0-3). The proportion of males presenting haemorrhagic manifestations was higher than females (Fisher Exact test; $p < 0.01$). Moreover, the age group 0-5 years presented a lower proportion of cases with haemorrhagic manifestations compared with the age group of 6 years and older ($p = 0.0281$). No significant differences were found between the diagnostic delays in the case of males and females.

Keywords: Dengue fever; Clinical diagnostic delay; Haemorrhagic; Colima; Mexico.

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Introduction

Annually there are approximately 100 million cases of dengue worldwide.^[1] It is endemic in Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific regions. The challenges seem daunting. For example, in Singapore, dengue is a major public health problem despite the fact that a set of extraordinary control efforts have been put into place over the past few years.^[2] The etiological agent is a *Flavivirus* with four different serotypes (DENV-1–4). The primary vectors of dengue are mosquitoes of the species *Aedes aegypti* and *Aedes albopictus*. Humans are infected when bitten by feeding infectious females. Those who recover may become permanently immune to the serotype involved and partially immune to the other serotypes.^[3] Susceptible vectors acquire the infection when feeding on infectious humans. Female mosquitoes are responsible for the transmission of the virus since males are non-blood suckers and feed primarily on plants and flowers.^[4]

Cases of dengue are classified as asymptomatic, clinically non-specific flu-like symptoms, dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).^[5] DHF and DSS are the severe forms of the disease. Dengue attack rates vary from 40% to 50% but may be as high as 80% to 90%.^[6]

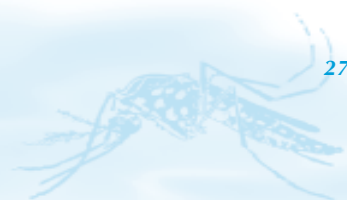
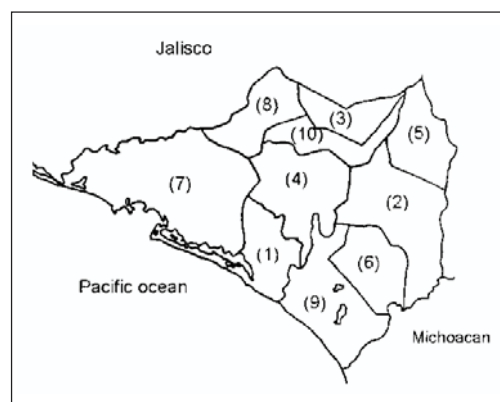
Mexico was declared dengue-free when the principal vector, *Ae. aegypti*, was eliminated in 1963. However, *Ae. aegypti* reappeared two years later and the disease returned.^[7] All the four dengue serotypes are now circulating in Mexico since 1980.^[7] DHF has become a public health problem in the country since 1994.^[8] In 2002, over 30 Latin American countries reported a total of over a million cases of classical dengue as well as more than 17 000

cases of DHF.^[9] We report the results of a retrospective study on the epidemiological and clinical characteristics of the 2002 (serotype DENV-2) dengue epidemic in the state of Colima, Mexico.^[10]

Materials and methods

The epidemiological and clinical characteristics of dengue fever cases recorded during the 2002 epidemic (January through December) in the state of Colima have been studied. The state of Colima is located on the Pacific coast, has a tropical climate, and has a population of 488 028 (Figure 1).^[11] The data used include cases diagnosed at the hospitals of the Mexican Institute of Public Health (IMSS). The IMSS are a collection of state hospitals that provide primary health services to 60% of the population in the state. The remaining population receives health care services from the hospitals of the Mexican Health Ministry and the private sector.

Figure 1: Map of the state of Colima, Mexico, with divisions by municipalities Armería (1), Colima (2), Comala (3), Coquimatlán (4), Cuauhtémoc (5), Ixtlahuacán (6), Manzanillo (7), Minatitlán (8), Tecomán (9), Villa de Alvarez (10)



Patient record data are stratified by municipality where the dengue cases were diagnosed (Figure 1); the week of symptom onset and diagnosis; the IgM antibody test result; patient's age and gender; and diagnostic delay (as presented later in the paper). Furthermore, non-haemorrhagic recorded symptoms included: fever, headache, myalgia, arthralgia, retro-orbital pain, exanthema, diarrhoea, vomit, nausea, pruritus, chills, photophobia, abdominal pain, conjunctivitis, nasal decongestion, cough, hepatomegaly and splenomegaly. Haemorrhagic recorded symptoms included: petechiae, ecchymosis, ascites, pleural effusion, gingivitis, epistaxis, haematemesis and melena. We classified a patient as "delayed" when clinical diagnosis was made two days after the onset of symptoms.

The World Health Organization (WHO) case definition of probable dengue cases^[3] requires the presence of fever or chills and at least two symptoms from: myalgia, arthralgia, retro-orbital pain, headache, rash, or some haemorrhagic manifestation (e.g. petechiae, haematuria, haematemesis, melena). The laboratory testing was only carried out in a small subset of the clinically diagnosed dengue cases through anti-dengue IgM antibody tests (ELISA).

We classified cases of DHF following as closely as possible all the four requirements for the WHO definition of DHF (fever, haemorrhage, thrombocytopenia, and signs of plasma leakage).^[6] Difficulties arose because basic measurements, such as platelet counts, were conducted in only 1227 (30%) of the cases and signs of plasma leakage were assessed only clinically (pleural effusion and/or ascites). The difficulties in characterizing DHF cases using the WHO system have led some investigators to use modified classification schemes.^[12,13] Here, we used the number of haemorrhagic symptoms as a measure of disease severity and classify dengue patients as haemorrhagic whenever one haemorrhagic symptom was reported. Dengue cases that did

not exhibit haemorrhagic manifestations were classified as non-haemorrhagic.

We characterize variations using the mean and standard deviation (SD). Proportions are compared using Fisher's exact test of independence, which uses a hypergeometric sampling distribution for cell frequencies.^[14] Population distributions are compared using the non-parametric Wilcoxon test. Results are deemed significant when the p value is less than 0.05. Some records are not complete. For example, the date of symptom onset was only recorded in 2242 patient records. Hence, the number of records (denoted by N) used is included in the analyses.

Results

The 2002 dengue epidemic in Colima, Mexico, began in January, peaked in September and died out in December (Figure 2). Four thousand and forty cases were clinically diagnosed, including 495 cases with haemorrhagic manifestations. A total of 555 clinical dengue cases (14%) were subjected to ELISA test and 548 cases were positive for anti-dengue IgM antibodies. Thrombocytopenia was detected in 528 cases but platelet counts were only recorded for 1227 cases (30%). Both thrombocytopenia and haemorrhagic symptoms were present in 203 cases (17%, N=1227), but only 8 cases could be classified as DHF under the WHO classification. The distribution of dengue cases by municipality is given in Table 1. The mean age of a dengue case was 24.61 ± 16.30 (SD) years (Figure 3A). The attack rate was about 9.5 dengue cases per 1000 persons. This rate was reported among two age groups of 5-14 and 25-34 years. The male/female ratio was about 1:1 with 2045 (50.6%) males and 1993 (49.4%) females. We found no significant difference between the age distribution of non-haemorrhagic and haemorrhagic cases (Wilcoxon test, $p=0.5018$, N=4007).



Figure 2: The weekly number of clinical haemorrhagic and non-haemorrhagic dengue cases during the course of the 2002 dengue epidemic in Colima, Mexico

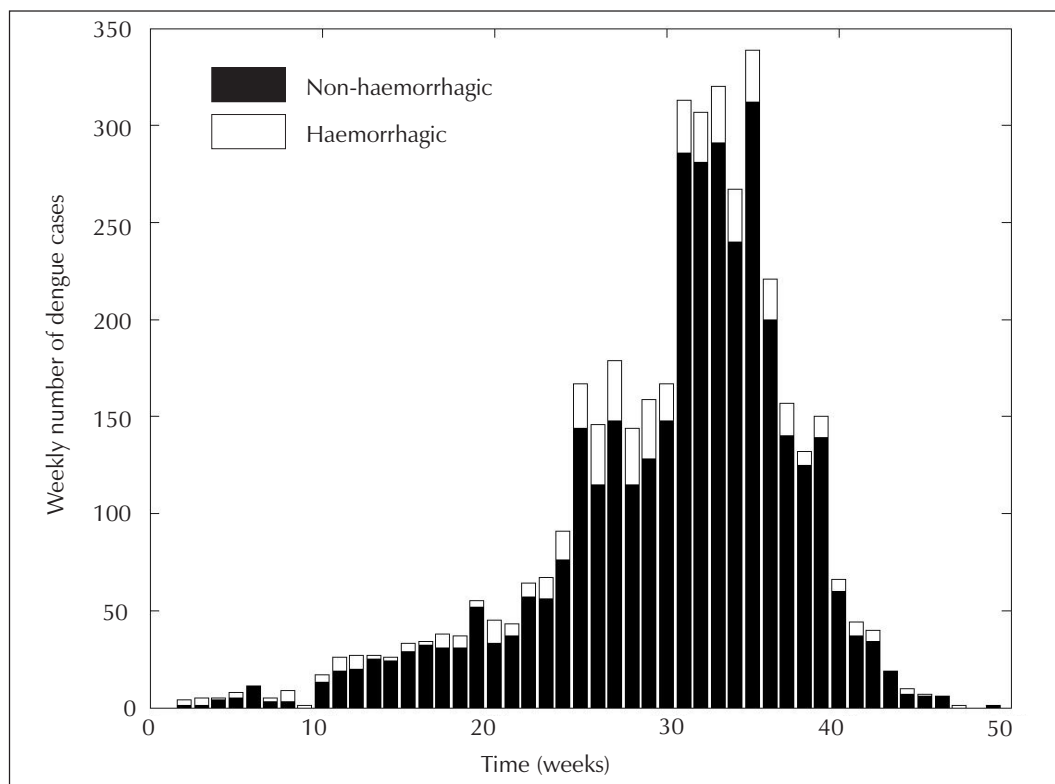
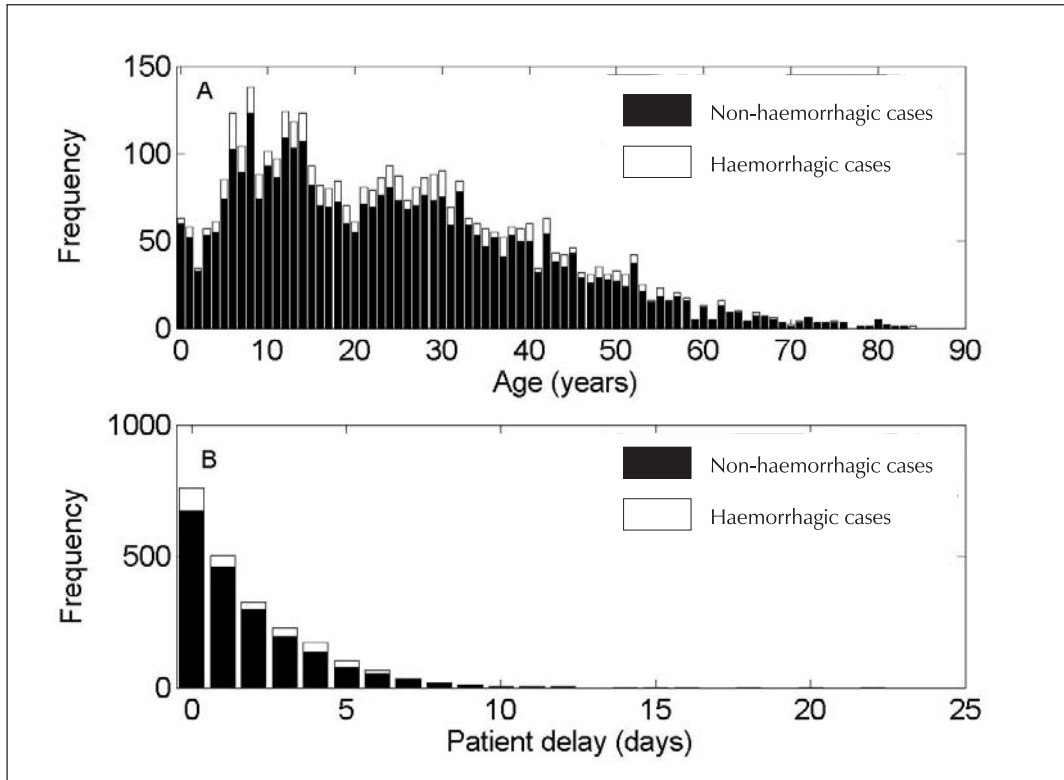


Table 1: Number of dengue cases reported by municipality and classified as haemorrhagic and non-haemorrhagic

Municipality	Population size	Total cases	Total cases per 1000 people	Haemorrhagic dengue	Non-haemorrhagic dengue
Armería	28 015	78	2.78	12	66
Colima	120 781	1167	9.66	169	998
Comala	17 601	17	0.97	4	13
Coquimatlán	16 939	94	5.55	11	83
Cuauhtémoc	25 462	114	4.48	8	106
Ixtlahuacán	4989	3	0.60	2	1
Manzanillo	108 584	1334	12.29	123	1211
Minatitlán	8321	4	0.48	3	1
Tecomán	91 036	338	3.71	35	303
Villa de Alvarez	66 300	891	13.44	128	763
Total	488 028	4040	8.28	495	3545



Figure 3: Age (A) and effective diagnostic delay (B) distributions of dengue cases presenting haemorrhagic and non-haemorrhagic manifestations during the 2002 dengue epidemic in Colima, Mexico



The most common symptoms in non-haemorrhagic dengue patients were fever (99.6%), headache (92.4%), myalgia (89.4%) and arthralgia (88.6%), while the least common symptoms were hepatomegaly (3.3%) and splenomegaly (2.3%). For haemorrhagic dengue cases, the median number of haemorrhagic manifestations was 1 (interquartile range [IQR]: 1-2) with a range from 1 to 7. The most common haemorrhagic manifestations were petechiae (7.1%), gingivitis (3.4%) and epistaxis (3.6%), while the least were ascites (0.3%) and pleural effusion (0.1%). The relative frequency of symptom appearance is displayed in Table 2.

The median diagnostic delay was 1 day (IQR: 0-3) with a range of 0 to 22 days (N=2242). Significant differences between the diagnostic delay distributions of non-haemorrhagic and haemorrhagic cases were obtained (Figure 3B, Wilcoxon test, $p=0.0004$, N=2242). In fact, the proportion of cases that experienced haemorrhagic manifestations and a diagnostic delay greater than two days was significantly higher than those with a diagnostic delay less than or equal to two days (17.4 vs 9.9%, $p<0.0001$, N= 2283; Fisher's exact test). The median diagnostic delay for haemorrhagic cases was 2 days (IQR: 0-4; range: 0-14) that is higher than for non-haemorrhagic cases, for which the median



Table 2: Frequency of clinical symptoms presented in dengue cases during the 2002 outbreak in Colima, Mexico
(Because some data were not completely recorded, we provide both the numerator (n) and denominator (N) used to compute the frequencies)

Characteristic	Positive, % (n/N)
Non-haemorrhagic manifestations	
Fever	99.6 (4009/4025)
Headache	92.4 (3707/4013)
Myalgia (muscle pain)	89.4 (3586/4010)
Arthralgia (joint pain)	88.6 (3550/4006)
Retro orbital pain	73.3 (2936/4004)
Chills	58.1 (2334/4018)
Nausea	52.5 (2107/4015)
Vomit	36.7 (1476/4023)
Photophobia	33.2 (1331/4006)
Abdominal Pain	32.4 (1299/4014)
Exanthema (skin rash)	30.3 (1217/4019)
Conjunctivitis (pink eye)	26.1 (1046/4010)
Pruritus (itching)	25.6 (1027/4015)
Diarrhea	18.3 (736/4019)
Cough	17.5 (702/4013)
Nasal decongestion	17.3 (694/4003)
Hepatomegaly (liver enlargement)	3.3 (128/3938)
Splenomegaly (spleen enlargement)	2.3 (90/3940)
Haemorrhagic manifestations	
Petechiae (small purplish spots)	7.1 (268/3761)
Epistaxis (nosebleed)	3.6 (136/3748)
Gingivitis (bleeding gums)	3.4 (126/3747)
Haematemesis (vomiting blood)	1.5 (58/3747)
Ecchymosis (bruising)	1.4 (52/3745)
Melena (blood in stool)	1.1 (41/3743)
Haematoma	0.6 (22/3746)
Ascites	0.3 (10/3741)
Pleural effusion	0.1 (5/3733)

diagnostic delay was 1 day (IQR: 0-3; range: 0-22). The proportion of cases with a diagnostic delay less than or equal to 2 days was significantly higher for children (≤ 15 years) than for adults (> 15 years) (73% vs 67%, $p=0.001$, $N=2283$, Fisher's exact test). No significant association between short diagnostic delay (less than or equal to 2 days) and gender ($p=0.36$, Fisher's exact test, $N=2281$) was found. The median diagnostic delay turned out to be 3 days (IQR: 0-4) ($N=114$) for cases with both haemorrhagic manifestations and thrombocytopenia.

A significant association between the presence of haemorrhagic manifestations and age was found. In fact, the 0-5 years age group supported a lower proportion of cases with haemorrhagic manifestations than the age group of 6 years and older (8.7 vs 12.7%, $p=0.0281$, Fisher's exact test, $N=4007$). A significant association between the presence of haemorrhagic manifestations and gender was also identified. In fact, the proportion of males (13.6%) with haemorrhagic dengue was higher than for females (10.8%) ($p=0.0072$; $N=4038$; Fisher's exact test).

Discussion

A retrospective study on the clinical and epidemiological characteristics of dengue was carried out during the 2002 epidemic in Colima. The levels of association significance were assessed between disease severity and epidemiological, clinical and demographic variables. We did not find a correlation between dengue disease and gender. The 1:1 female/male ratio is in agreement with other dengue studies conducted in Nicaragua,^[15] Thailand^[16] and Taiwan.^[17] Males in our study were statistically more likely to experience haemorrhagic manifestations, a finding that agrees with a study conducted in Nicaragua.^[15] We found a significantly higher median



diagnostic delay for cases presenting haemorrhagic manifestations than for non-haemorrhagic cases.

Not surprisingly, this finding indicates an important correlation between the disease's clinical evolution and diagnostic delay. Diagnostic delays may complicate the clinical state of the patient while facilitating the transmission of dengue in the population. In other words, although interventions have shown to be incapable of reverting a dengue epidemic,^[18] reductions in the diagnostic delays can reduce the final epidemic size. Mathematical models of dengue transmission have shown that educational campaigns aiming at shortening the diagnostic delays can lead to significant reductions in the final epidemic size.^[19] Control strategies that benefit from a prompt identification of dengue cases include the use of nets and screens, the application of insecticides to clothing and the application of mosquito repellents. Moreover, strategies aiming at the elimination or reduction in the number of breeding sites through the use of larvicidal control including ovitraps^[20] and malathion spraying for adult control can also reduce the dengue burden.

A fever alone is usually not enough to motivate patients to seek medical care. It is only the presence of severe symptoms (e.g. haemorrhagic manifestations) that motivate to seek medical care. This observation may explain the significant association that we found between diagnostic delays and the presence of haemorrhagic manifestations. Specifically, we found that the proportion of cases with a diagnostic delay of less than or equal to 2 days was significantly higher for children (≤ 15 years) than for adults (> 15 years). This is in agreement with the findings by Ahorlu et al.^[21] who studied the socio-cultural determinants of treatment delay for childhood malaria in southern Ghana. Ahorlu et al.^[21] found that families with similar economic situations who have sick children will

be more likely to seek treatment. Gender exhibited no correlation with the length of the diagnostic delays. The most common explanations for diagnostic delays in malaria studies in sub-Saharan Africa include poverty and the inability to pay for treatment.^[22] This perspective could not be assessed here as most of the patients comprised only the insured individuals by IMSS. In summary, a combination of cultural factors, the inability to distinguish dengue illnesses from traditional fevers at the early stages of the disease, and the differentiated treatment are the main factors behind differences in diagnostic delays.

The impact of dengue diagnostic delay distributions and their association with clinical, demographic and epidemiological factors have not received much attention. This contrasts, for example, with epidemiological studies dealing with other infectious diseases such as pulmonary tuberculosis.^[23] However, there are some relevant studies. For example, an estimate of the median diagnostic delay of 5 days has been reported for the 1996 dengue epidemic in north-eastern Brazil,^[24] that is, a significantly longer median diagnostic delay than our estimate of 1 day. Guzman et al.^[25] found that the average time from fever onset to hospitalization associated with the 1997 dengue outbreak in Cuba was about 2.9 days. On the other hand, a median diagnostic delay of 2 days was reported for malaria-stricken travellers returning to Sweden during 1994 to 2001.^[26]

We found a lower proportion of haemorrhagic cases in the age group 0-5 years than those in the age group of 6 years and older. Secondary dengue infections have been associated with the presence of haemorrhagic manifestations, a phenomenon explained by the theory of antibody-dependent enhancement.^[5]

Seasonal effects are also critical. The peak of the epidemic in Colima occurred in mid-September, which correlates well with the



peak in the rainfall.^[27] A similar pattern has been reported for other dengue outbreaks {Nicaragua (1998),^[15] El Salvador (2000)^[28] and Bangladesh (2000)^[29].

In contrast to dengue hyperendemic areas where dengue haemorrhagic fever is primarily a disease of children under 15 years, we found a lower proportion of haemorrhagic cases in the age group 0-5 years compared to the age group of 6 years and older.

The number of dengue infections per municipality was determined by the location of the patient's address albeit the actual dengue infection may have occurred at work because dengue mosquitoes are daytime feeders.^[30]

This study was limited by the lack of complete medical records. Difficulties were encountered in rigorously following the WHO classification scheme for DHF, because the signs of plasma leakage were assessed only clinically (pleural effusion and/or ascites). The number of DHF cases may in fact be as high as 203, that is, the number of cases for which the other three requirements of the WHO classification scheme for DHF (fever, haemorrhage and thrombocytopenia) were satisfied. On the other hand, dengue cases with severe haemorrhage, not accompanied by increased vascular permeability, have been reported from several regions of the world

including Indonesia, China, India, Philippines, Thailand, South Pacific and Latin America.^[31] To improve the tracking of dengue, workers at IMSS hospitals would need to collect as complete patient information as possible. Efforts to follow the WHO classification guidelines as closely as possible would be quite helpful. Dengue symptoms can be confused in the epidemic and non-epidemic situations with other exanthematous and non-exanthematous viral diseases such as measles, rubella, enteroviruses and influenza.^[31] We recognize that there are limited resources for laboratory testing. In the 2002 dengue epidemic in Colima, only 14% of the clinical dengue cases were tested in the laboratory for anti-dengue IgM. The low proportion of clinical dengue cases tested serologically make it difficult to validate some of our findings.

Our findings indicate that an educational campaign in the community with the objective of informing the population about early symptoms of dengue infection could lead to not only reductions in diagnostic delays but also to reduce the final size of a dengue epidemic.

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