

# Clinical Pattern of Hospitalized Patients during a Dengue Epidemic in Colima, Mexico

**Francisco Espinoza-Gómez\***<sup>✉</sup>, **Porfirio Díaz-Dueñas\*\***, **Claudia Torres-Lepe<sup>†</sup>**,  
**Ramón Arturo Cedillo-Nakay<sup>\*</sup>** and **Oscar Alberto Newton-Sánchez<sup>\*</sup>**

*\*Francisco Espinoza- Gómez, Facultad de Medicina, Universidad de Colima, Av. Universidad 333, Colonia Las Víboras, Colima, Colima México C.P. 28040*

*\*\*Delegación Colima del Instituto Mexicano del Seguro Social*

*<sup>†</sup>Hospital Regional Universitario del Estado de Colima, Secretaría de Salud, México*

## Abstract

During 2002, a dengue epidemic was recorded in the Mexican state of Colima, located on the western coast. In this study the data released by the state of Colima's Health Secretary in 2002 is analysed. In addition, medical files of 1079 patients hospitalized with the diagnosis of dengue during the same year were reviewed with the purpose of exploring the clinical and demographic characteristics of the epidemic outbreak. During 2002, 1766 cases of classic dengue and 617 cases of haemorrhagic dengue (DHF) were identified by the Health Secretary of Colima. Of the 1079 patients hospitalized, the diagnosis of dengue was confirmed by laboratory testing in 289 of the patients. The majority of them presented clinical characteristics consistent with DHF, 52 showed signs of liver damage, 6 of encephalitis and 4 with acute respiratory distress syndrome. Three of the patients were newborns and a total of six died of consequences attributed to dengue (0.8%). DENV-2 was isolated in 12 cases. The presence of this unusual outbreak of dengue, accompanied by complications unknown in this region as well as vertical transmission and fatal cases, should alert the health authorities to the importance of maintaining more efficient dengue vigilance systems before the possibility of a growing phenomenon that can affect *Aedes aegypti*-infested communities, even when preventive programmes are put into action.

**Keywords:** Dengue, dengue haemorrhagic fever, Colima, Mexico.

## Introduction

Without doubt, dengue continues to be a great challenge for public health, and, in spite of the opportune application of vector control strategies, significant epidemic outbreaks are observed year after year in different parts of the world. These outbreaks result not only in loss of human life but also in enormous economic costs in affected communities<sup>[1]</sup>. Despite the fact that in Mexico, as in a majority of endemic countries, preventative actions are

punctually employed<sup>[2]</sup>, dengue continues to reappear in violent outbreaks accompanied by increasingly severe complications. This phenomenon could be attributed to increased sensitivity of the vigilance systems in detecting the aforementioned complications or to the outbreaks escalating to more aggressive clinical patterns, possibly due to the periodic circulation of new serotypes in communities previously exposed to other serotypes, or to the appearance of more virulent viral strains in the Americas<sup>[3]</sup>.

<sup>✉</sup>fespin@cgcic.ucol.mx; <sup>☎</sup>/Fax (52) 312 31 610 99



The state of Colima, on the Pacific coast of Mexico, is an area permanently infested by *Aedes aegypti*, with endemic transmission of dengue<sup>[4]</sup>. In 1997, there was an outbreak attributed to dengue, with some cases of dengue haemorrhagic fever (DHF). This phenomenon repeated itself in 2002, but on this occasion was accompanied by an unexpected amount of DHF cases, some of which were fatal, as well as by complications that up until that time were unknown in Mexico. During this epidemic the Mexican authorities recognized 13 131 cases of classic dengue and 2159 of DHF. Meanwhile, in Colima, 9003 possible cases of dengue were identified, of which 1766 were confirmed as classic dengue and 613 as DHF<sup>[5,6]</sup>. The purpose of this study was to describe the clinical and epidemiological characteristics of patients hospitalized in public health services of Colima during this outbreak, focusing on the age distribution of the cases and in the presence of complications previously unrecorded in this part of the country.

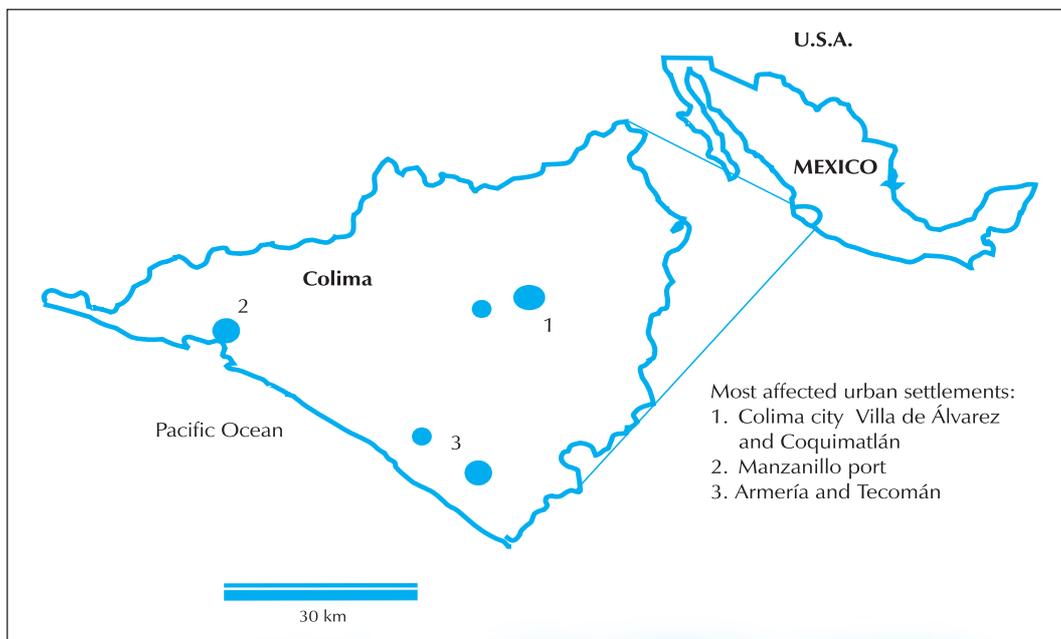
## Materials and Methods

This is a case series study in which information about patients diagnosed as classic dengue and DHF, attended at the public hospitals of the state of Colima, México, were reviewed.

The state of Colima is located on the Pacific Mexican coast between 18° 55' and 19° 23' NL and 103° 36' to 104° 19' WL (Figure 1), with a population of 542 627 inhabitants<sup>[6]</sup>. The climate is warm with an annual median temperature of 24.5 °C and an annual pluvial precipitation of 910 mm (data from the Comisión Nacional del Agua, Colima delegation).

The patients included in the study were hospitalized during 2002 in hospitals belonging to the Secretary of Health of the state of Colima (Hospital Regional Universitario de Colima) and the Instituto Mexicano de Seguro Social (IMSS), in the cities of Manzanillo, Tecoman,

Figure 1. Mexico and the state of Colima



Cuauhtemoc and Colima. The involved hospitals have 477 beds and cover approximately 75% of the state's population<sup>[6]</sup>. In each patient, age, sex, place of residence, the date of the initiation of fever, medical conditions and at what point in the evolution of the fever the blood sample was taken, were registered. The clinical classification of hospitalized cases was done according the WHO recommendations as: classic dengue with unusual haemorrhage manifestations (CDHM), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) when a clinical picture of DHF was accompanied by hypotension, cold clammy skin and rapid and weak pulse<sup>[2,7,8]</sup>. For this clinical classification, the results of tourniquet test, platelet count, haematocrit, haemoglobin, hepatic enzymes: alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were also recorded.

In the evaluation of the laboratory results we considered only those cases in which the sample was taken at the correct time (less than five days for viral identification and between 6 and 30 days for IgM detection). The viral identification was done by reverse-transcriptase, polymerase chain reaction (RT-PCR), following the procedures suggested by Chang et al.<sup>[9]</sup>. Meanwhile, the serotype was determined by an indirect immunofluorescent test (IIF) with specific monoclonal antibodies donated by the Division of Vector-Borne Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, Colorado, USA.

The search for anti-dengue IgM antibodies was realized with the MAC ELISA test (Light Chemicon, Temecula Ca.) or with rapid immunochromatography (Rapid Pan-Bio test, Brisbane, Australia). Some sera were also tested for IgG anti-dengue antibodies with these same techniques. In all cases, the results were dichotomous: positive or negative, depending on the manufacturer's specifications.

The RT-PCR, the IIF, as well as most of the MAC ELISA tests were conducted at the Instituto Nacional de Referencia Epidemiológica (INDRE) in Mexico City; meanwhile, some of the MAC ELISA and all of the rapid immunochromatographic tests were done at the Faculty of Medicine of the University of Colima.

## Results

During 2002, approximately 23 500 people were hospitalized in the studied medical units, 1378 were discharged with a clinical diagnosis of dengue with some complication; it could be classic dengue with unusual haemorrhage manifestation (CDHM), DHF or DSS. From these 1378 cases, 450 were diagnosed clinically as CDHM; meanwhile, 928 cases fulfilled the four requisites for a clinical diagnosis of DHF or DSS<sup>[7,8]</sup>. In 340 of the total cases, it was possible to obtain a reliable serum sample. Of them, 22 resulted positive for virus identification by the RT-PCR technique, and in twelve sera it was possible to isolate DENV-2 by the IIF technique. In the remainder 10 cases, the serotype was not reported. In 7 patients, paired samples resulted positive to anti-dengue IgM, while in 260 cases there was only an isolated determination positive for IgM. For this reason they were classified as "probable" dengue according the Pan American Health Organization's and WHO's criteria<sup>[7]</sup>. Nevertheless, for this study, the whole 289 serum-positive cases, which constituted 85% of the samples taken in the correct time period for diagnosis, were considered as confirmed dengue infection and were included in the description as CDHM (23 cases), DHF (261 cases) and DSS (5 cases).

Table 1 shows the distribution of all the patients hospitalized in 2002 in the public hospitals of Colima and those diagnosed as dengue, as well as their laboratory results, according the attending institution.



**Table 1.** Total of patients hospitalized in the public hospitals of Colima during 2002 and those with a clinical diagnosis of dengue

Institution	Number of beds	Total hospital discharges	Sera examined for dengue infection	IgM positive	RT-PCR positive
HRU <sup>a</sup>	147	7574	204	152	18
IMSS <sup>b</sup>	230	16 351	136	115	4
Total	377	23 925	340	267	22 <sup>c</sup>

<sup>a</sup> Hospital Regional Universitario de Colima (Ministry of Health)

<sup>b</sup> Instituto Mexicano del Seguro Social (Mexican Institute of Social Security)

<sup>c</sup> DENV-2 identified in 12 cases, no other serotype was identified. In total 289 cases positive for dengue infection (85%)

The clinical pattern of the 289 patients with positive test for dengue and their most relevant signs are shown in Table 2. As can be noted, bleeding was the major clinical complication and the most frequent sources of haemorrhage were: nose, gums, upper and lower gastrointestinal tract, uterus, urinary tract and skin, in that order. However, only two patients required blood transfusion for severe haemorrhage. Hepatomegaly accounted in 15 patients; meanwhile, 9 cases showed altered hepatic enzymes (AST and ALT), although this later laboratory test was carried out only in 127 patients. From all the patients with hepatic abnormalities, only 3 showed frank jaundice and 4 had fulminant hepatitis; two of them died.

Four patients developed encephalitis, characterized by mental deterioration (Glasgow score between 7 and 11) or seizures, all of which showed an elevated white cell count (10 to 25 white cells/ml) and protein concentration in cerebrospinal fluid (600 to 1540 mg/ml), without evidence of hyponatremia, bacterial, fungal or mycobacterium infection, although in no one of them the cerebrospinal fluid was examined for dengue tests.

The clinical characteristics of the 6 patients with confirmed dengue who died are described

in Table 3. As can be noted, 3 cases were diagnosed as DHF and 3 cases as DSS, accompanied with complications as pure encephalitis (case 1), encephalitis in the setting of multiple organ dysfunction syndrome (case 3); fulminant hepatitis with hepatic failure in this same patient and in the other with exclusive hepatic failure (case 2). Massive gastrointestinal bleeding with hypovolemic shock was diagnosed in two patients (4 and 5); and a purpuric syndrome associated to DSS in a newborn, who developed a large cerebral haematoma and whose mother was diagnosed as DHF.

The post-mortem examination of the patient with multiple organ dysfunction syndrome (number 3) revealed focal hepatic necrosis, cerebral edema with areas of necrosis, microhaemorrhages and microthrombosis, with scarce inflammatory activity, while the RT-PCR study did not show evidence of the dengue virus in the brain. This same patient presented acute tubular necrosis and diffuse pulmonary infiltration compatible with adult respiratory distress syndrome. No belated complications were documented in any of the other patients, all of whom completely recovered from the acute symptoms within two to four weeks, including those with DSS, hepatitis or encephalopathy.



**Table 2.** Clinical pattern of hospital patients diagnosed as classic dengue with unusual haemorrhage manifestations (CDHM), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS)

Clinical parameters	CDHM n= 23	% in CDHM	Dengue haemorrhagic fever n= 261	DSS n= 5	% in DHF and DSS
Thrombocytopenia (< 100,000/ mm <sup>3</sup> )	11	47.8	261	5	100.0
Positive tourniquet test	2/18	11.1	67/245	4	28.4
Bleeding <sup>a</sup>	8	34.7	195	4	63.5
Haemoconcentration <sup>b</sup>	0	0	181/261	4	69.5
Pleural effusion	0	0	19	2	7.9
Ascitis	0	0	18	3	7.9
Hypoalbuminemia	2/19	10.0	43/192	3	23.6
Hepatomegaly	2	8.7	11	3	5.2
Elevated ALT and/or AST <sup>c</sup>	1/14	7.1	5/108	3	7.0
Fulminant hepatitis	0	0	2	2	1.5
Encephalitis <sup>d</sup>	0	0	2	2	1.5
Acute respiratory distress syndrome <sup>e</sup>	0	0	2	1	1.1
Laboratory confirmation <sup>f</sup>	2 RT-PCR 21 IgM		19 RT-PCR 242 IgM	1 RT-PCR 4 IgM	
Deaths	0	0	3	3	2.2

<sup>a</sup> From the total of 207 patients with bleeding, 177 showed frank clinical blood losses (epistaxis, gingivorrhagia, haematemesis, melaena, methrorrhagia, haematuria), the remaining patients had only mild and transitory bleeding.

<sup>b</sup> Reduction in haematocrit > 20% after fluid replacement; or Hct/ Hb ≥ 3.3

<sup>c</sup> 12 patients with both: hepatomegaly and elevation of AST and ALT.

<sup>d</sup> Diffuse encephalopathy with abnormal cerebrospinal fluid (pleocytosis, elevated proteins), without major metabolic disorder.

<sup>e</sup> Clinical and radiological evidence of diffuse lung infiltration with acute respiratory insufficiency in the absence of pneumonia or cardiac failure.

<sup>f</sup> In total 340 patients were adequately sampled; 267 resulted positive for IgM and 22 for RT-PCR.

Figure 2 depicts the distribution of the hospitalized cases diagnosed as confirmed dengue infection by gender and age group, which, on average, was 23.3 years in 137 females and 21.6 years in 152 males (ranging from 1 day to 74 years). Three newborns (2 male and one female) with clinical picture of DHF are included here (one of them died with DSS).

It should be mentioned that IgG was determined in 28 of the 227 IgM seropositive patients with a clinical diagnosis of DHF; of them, 20 resulted positive and 8 IgG negative (the latter suggestive of primary infection).

In Figure 3, it is possible to appreciate the distribution of the cases of confirmed dengue per month in the state during 2002. The first



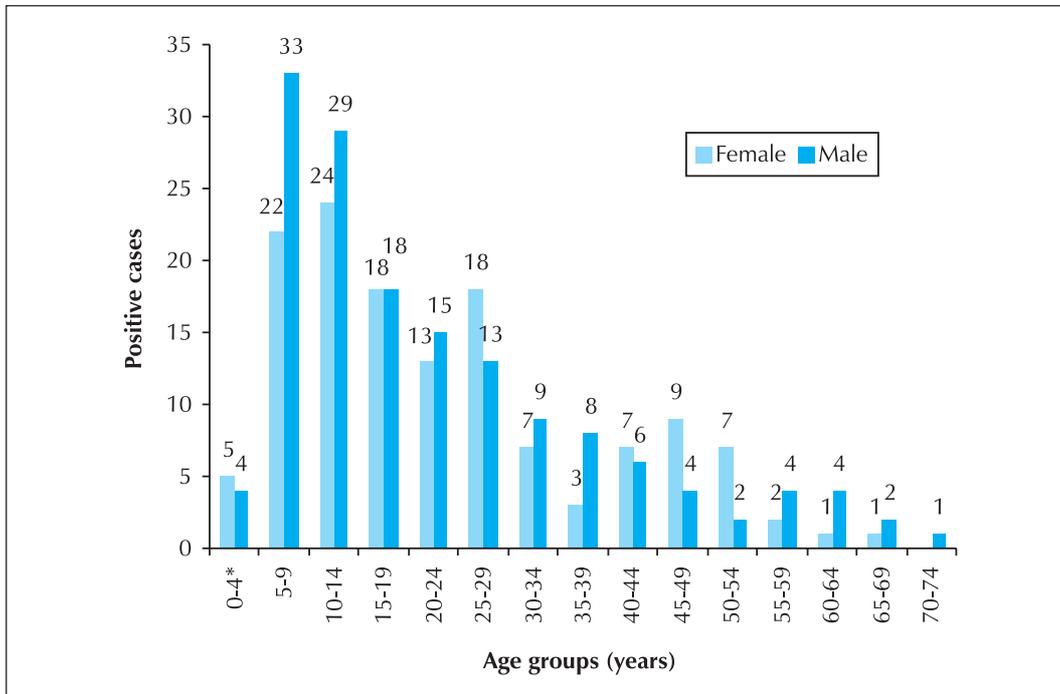
**Table 3.** Patients who died during the outbreak due to DHF and DSS

Patient (chronology)	Sex	Age	Institution**	Clinical classification	Cause of death	Date of death
1	F	10	HRU	DHF	Encephalitis	14 Jun 2002
2	M	10	IMSS	DSS	Fulminant hepatic failure	12 Aug 2002
3	M	26	HRU	DSS	Multiple organic failure*	20 Aug 2002
4	F	6 months	HRU	DHF	Gastrointestinal bleeding	16 Sep 2002
5	M	64	IMSS	DHF	Gastrointestinal bleeding	21 Sep 2002
6	M	Newborn	HRU	DSS	Purpura, cerebral haematoma	02 Oct 2002

\* Autopsy findings described on text

\*\* Names of institutions described under Table 1

**Figure 2.** Distribution of hospitalized cases with confirmed dengue, according to sex and age group

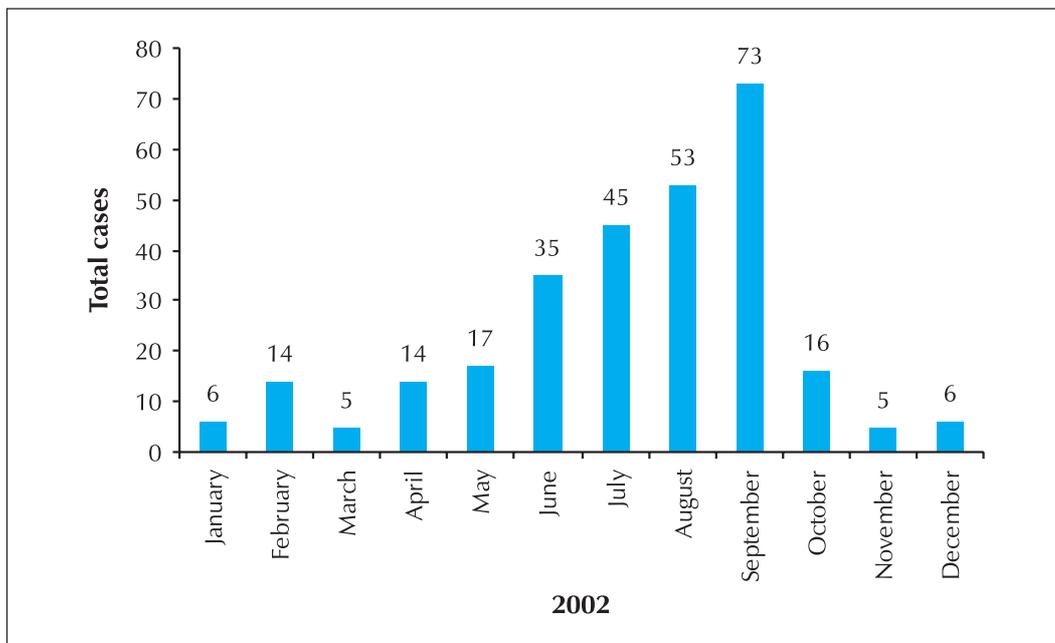


Pearson's  $\chi^2$  adjusted by age group male vs female = 1.75,  $P=0.14$

\*In total 3 cases of DHF in newborns (2 males and one female)



Figure 3. Monthly distribution of hospitalized cases with confirmed dengue during 2002 in Colima



cases of DHF were reported in the Manzanillo port in January, reaching a maximal incidence in June, with expansion to the neighbouring cities of Armería and Tecomán (Figure 1). Meanwhile, the maximum peak of transmission was observed in the urban zone of the city of Colima and Coquimatlán, remaining until August and September, and disappearing abruptly in November.

## Discussion

The appearance of dengue epidemics, accompanied by DHF and other complications, is no novelty in endemic countries such as Mexico and others in Central America and the Caribbean, where significant epidemics have been registered recently<sup>[10,11]</sup>. Nevertheless, the epidemic in 2002 was greater and more severe than those previously documented<sup>[12]</sup>.

This is a reason for particular concern, because either the preventive programmes

have not been as effective as expected<sup>[13]</sup>, or there is a possible appearance of more virulent strains in the region<sup>[3,14]</sup>.

In this epidemic in Colima, 2379 cases of dengue infection, 617 of which were DHF, were officially confirmed. This represents a very elevated attack rate (approximately 4.3%), although it is possible that the number of people infected by dengue in the region was actually higher during the year in question, taking into account that many patients were not adequately studied, as is shown in the analysis of hospitalized patients where it was discovered that in only 30% of suspected cases of dengue, laboratory testing was done at the right time. This situation should alert the epidemiological surveillance systems in the area to be better prepared for timely and reliable detection of new dengue infections.

The presence of DHF and DSS has been attributed to an exaggerated immune response



produced when there is a secondary heterotypic infection in an individual previously sensitized against a different serotype, in a phenomenon known as antibody-dependent enhancement<sup>[15]</sup>. In the present epidemic, the presence of patients with DHF indicated the circulation of a new serotype in a population previously exposed to heterotypic infections, as is the case of Colima where at least two serotypes have been recognized in the past with a continuous inter-epidemic transmission<sup>[4,16]</sup>. Nevertheless, the presence of eight DHF cases negative to IgG (primary infection) suggested that at least some of the DHF in the present epidemic was caused by the introduction of a new, more pathogenic strain of DENV-2 in the region, as has been proposed by some authors<sup>[3,14,17]</sup>.

The proportion of hepatomegaly and liver dysfunction in this study was lower than usually reported<sup>[10,18]</sup>, but similar to recent findings in patients with DHF in México<sup>[12]</sup>. Meanwhile, complications such as encephalitis and pneumonitis by dengue are no different than that of recent dengue epidemics at other latitudes<sup>[19,20]</sup>, although this is the second incidence of encephalitis associated with dengue in the country<sup>[21]</sup>, and the first time in the western part of Mexico that deaths attributed to dengue had been identified, even though with a fatality rate similar to other reports in the region<sup>[12]</sup>. All these findings should alert clinical physicians in Mexico to the growing possibility of observing cases of dengue manifested with these unusual complications and not only the traditional pattern of fever, rash and bleeding.

It is possible that the presence of such unpublished complications is due to the fact that on this occasion the medical services were more alert to the possibility of the aforementioned conditions. However, a better explanation for this phenomenon is the persistent use of obsolete strategies like massive fumigations during the emergence of epidemics, performed by the majority of Latin American countries, actions that have shown to be largely expensive and inefficient<sup>[13,22]</sup>.

In this epidemic the most affected age group was older than normally reported in dengue epidemics. This last finding could be explained in part by an insufficient clinical suspicion of complicated dengue among paediatric patients in Mexico, although this discovery could be part of a phenomenon recently reported in other parts of the world, including México, where DHF has shown a tendency towards affecting an increasingly older population group<sup>[12,17,23]</sup>. On the other hand, this is the first report of neonatal dengue in México.

The peak transmission during August and September coincides with the maximum pluvial precipitation combined with higher environmental temperatures in the state of Colima, a combination previously reported to be associated with higher *Aedes aegypti* populations in the area<sup>[24]</sup>.

Dengue and its most serious forms, DHF and DSS, as well as unusual complications seem to be poorly controlled as of now in the Americas, despite extensive development of traditional preventative programmes<sup>[13,22]</sup>. This should alert the global community to assign more resources to the maintenance of sustainable entomological and epidemiological surveillance programmes based on community participation, improvement of dwelling conditions as well as more training for medical workers in reference to tropical diseases, especially in countries infested with *Aedes* mosquitoes.

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