From primary care to hospitalization: clinical warning signs of severe dengue fever in children and adolescents during an outbreak in Rio de Janeiro, Brazil

Da atenção primária à hospitalização: sinais clínicos de alarme para dengue grave em crianças e adolescentes durante uma epidemia no Rio de Janeiro, Brasil

De la atención primaria a la hospitalización: señales clínicas de alarma del dengue grave en niños y adolescentes durante una epidemia en Río de Janeiro, Brasil

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Abstract

We analyzed factors associated with severe cases of dengue in children and adolescents hospitalized during the 2007/2008 epidemic in Rio de Janeiro, Brazil. This is a retrospective case-control study that covers 88 cases of severe dengue in patients admitted to four tertiary care children's hospitals. Controls consisted of 22 children with non-severe dengue living in the same neighborhood as the patients with severe dengue. Differences in prevalence of the clinical signs – abdominal pain, breathing difficulty, drowsiness or irritability – emerged on the third day after the onset of symptoms, in the febrile stage. Cases and controls received first medical care at the same clinical stage of disease. However, hospital admission of severe cases occurred later, on average between the third and fourth day after the onset of the disease. Early discharge of patients with fever whose condition could have progressed to severe dengue may have been a consequence of the type of medical assistance provided by primary care units, suggesting deficiencies both in the use of the risk classification protocol and patient triage.

Dengue; Epidemics; Signs and Symptoms

Resumo

Foram avaliados fatores associados à ocorrência de casos graves de dengue em crianças/adolescentes hospitalizados durante a epidemia de 2007/2008 no Rio de Janeiro, Brasil. Trata-se de estudo caso-controle retrospectivo com 88 casos graves de dengue, admitidos em quatro hospitais de atenção terciária infantil. Os controles foram 22 crianças com dengue não grave residentes na vizinhança dos casos. Foram observadas diferenças na prevalência de sinais clínicos – dor abdominal, dificuldade respiratória, sonolência/irritabilidade – a partir do terceiro dia do início dos sintomas, ainda na presença da febre. Casos e controles receberam o primeiro atendimento médico no mesmo estágio clínico da doença. Contudo, as hospitalizações dos casos graves ocorreram mais tardiamente, em média entre o terceiro e quarto dia da doença. A liberação precoce de pacientes com quadro febril e potencialmente graves pode ter sido consequência do atendimento médico prestado nas unidades de atenção primária, sugerindo deficiências na aplicação do protocolo de classificação de risco de dengue e triagem de pacientes.

Dengue; Epidemias; Sinais e Sintomas

Background

The recent change in the epidemiological profile of dengue in some Brazilian cities has reinforced the importance of this endemic disease as a Public Health issue. Such changes are characterized by the emergence of severe forms of the disease in younger age groups and the ensuing increase in hospital admission and case-fatality rates [1,2].

In the city of Rio de Janeiro, the occurrence of severe dengue among younger individuals became evident between 2007 and 2008 when the city experienced an alarming epidemic of severe dengue that disproportionally affected individuals under 15 years of age [3,4,5,6]. Approximately 322,000 cases were notified during this period. A total of 240 deaths occurred, of which 100 were due to hemorrhagic fever and 140 were attributed to complications resulting from dengue [7].

The city had been previously affected by three major dengue epidemics: the first in 1986, caused by the serotype DENV1 [8]; the second in 1991 due to the serotype DENV2 when the first cases of hemorrhagic dengue fever were confirmed [9,5,10,11]; and the third that occurred between 2001 and 2002, this time attributed to the introduction of the serotype DENV3, where the number of notified cases exceeded 288,000. Although 1,831 cases of hemorrhagic fever and 91 deaths were reported during the 2001/2002 epidemic, it was only during the 2007/2008 epidemic that severe cases in younger individuals became evident [3,4,5,12,13].

Currently there is no precise method for early prediction of disease severity [14]. Recognizing the signs of progression to the severe form of the disease during the initial febrile phase – which lasts between two and seven days – may be difficult in children as symptoms are often indistinguishable from other acute febrile diseases. Severity usually becomes apparent in the critical phase, when a sudden drop in temperature associated with clinical and laboratory manifestations of endothelial dysfunction (increased capillary permeability and plasma leakage) indicate a clinical alert [15,16].

The role of clinical and laboratory diagnosis and treatment as one of the factors that contributed to the severity of the 2007/2008 epidemic has become a matter of debate. In this respect, the early recognition of the clinical features of the disease for predicting severity during the triage process is essential for an effective treatment planning protocol and thus for the recovery of potentially severe and fatal cases.

The aim of this study was to assess factors associated with the occurrence of severe dengue and evaluate early signs and symptoms related to the clinical evolution of the disease before hospitalization. Severe cases, defined here as children and adolescents hospitalized in four tertiary children's hospitals during the 2007/2008 epidemic in Rio de Janeiro, were compared with household controls that had non-severe dengue fever.

Material and methods

For this case-control study 88 severe cases were selected from all patients up to 18 years of age hospitalized between 1st November 2007 and 30th April 2008 in four tertiary children's hospitals in the city of Rio de Janeiro, Brazil. We selected 367 possible controls residing in the same city block as the severe cases and matched by age (with a maximum three year age difference). Of this group, only 22 presented non-severe dengue, defined by a positive serological diagnosis of dengue infection, and were therefore considered the controls for the present study.

Selection and eligibility criteria

- **Cases**

Severe cases were identified based on a review of medical records in the participating hospitals and defined as having shock syndrome (the clinical syndrome that results from inadequate tissue perfusion) [17] i.e.; presence of either hypotension (defined as systolic pressure < 80mmHg for patients aged < 5 years and < 90mmHg for those aged ≥ 5 years) or narrow pulse pressure (difference between systolic and diastolic pressure ≤ 20 mmHg), associated with at least one of the following signs: cold clammy skin, slow capillary filling or filiform pulse. The inclusion criteria were patients clinically diagnosed with dengue (classified as severe dengue) in the two to 18 year age group . The patients were hospitalized between 1st November 2007 and 30th April 2008 in the intensive care units (ICU) of the following tertiary care children's hospitals: the Martagão Gesteira Institute for Childcare and Pediatrics, Rio de Janeiro Federal University (IPPMG/UFRJ, acronym in Portuguese); the Fernandes Figueira Institute, Oswaldo Cruz Foundation (IFF/Fiocruz, acronym in Portuguese), Pronto Baby Hospital and Menino Jesus Hospital. Due to logistics and costs reasons, serological confirmation and virus isolation is not routinely performed during an epidemic situation [18], thus we were not able to consider these tests as inclusion criteria; however 49 of the 88 severe cases showed positive IgM-class immunoglobulins and all cases were IgG positive when the clinical-epidemiological diagnosis of dengue was validated.

Most of the severe cases were from the city of Rio de Janeiro (69.3%); however 30.6% were from other cities in the State of Rio de Janeiro (Duque de Caxias, Mesquita, Magé, Niterói, Nilópolis, Nova Iguaçu and São João do Meriti), since the participating hospitals are referral centers for children.

• **Controls**

For each case we sampled at least four possible controls from different households. The search for households to identify possible controls obeyed the following order: (i) First household to the right of the visited home; (ii) First household to the left of the visited home; (iii) First household in front of the visited home; (iv) Second household to the right of the visited home; (v) Second household to the left of the visited home; and so on until the total number of possible controls had been reached. For apartments, the same process was followed by floor and the procedure was repeated one floor below and one floor above until the necessary number had been reached.

We selected 367 children as possible controls living in the same city block as the respective severe case and with a maximum age difference of three years. The control group comprised 22 children from this larger group who had non-severe dengue (and were not hospitalized) diagnosed at health care units and showing a positive serological test for dengue fever during the same epidemic period.

Non-inclusion criteria

Children with hematologic or neoplastic disorders, autoimmune diseases and immunodeficiencies, including transplants and HIV positive [17], were not eligible for the study. Also, children hospitalized due to dengue fever were not eligible as control subjects.

Study procedures and laboratory diagnosis

We conducted interviews with the legal guardians of both cases and possible controls during home visits. On the same occasion we collected blood samples to carry out serological tests. *Dengue virus-s*pecific IgGs were measured in the serum samples from the whole sampled population using a commercial dengue indirect IgG enzyme immunosorbent assay (ELISA) kit (Panbio). The results of this test are classified as positive, negative or inconclusive.

In addition to socio-demographic data, the questionnaire contained questions regarding history of previous dengue infection. For both cases and controls we also collected data regarding the search for medical assistance and daily evolution of clinical symptoms, listed as the following negative prognostic indicators: hemorrhagic manifestations (any type of bleeding), abdominal pain, breathing difficulties and irritability and/or drowsiness. Although fever is not normally considered as a warning sign, it was also included in the analysis because the end of the high fever period may be a marker of early critical phase of the disease.

Data analysis

Data from the completed questionnaires was inputted using Epidata software (Epidata Association, Odense, Denmark) and statistical analysis was performed with the statistical software R 2.9.2 and epicalc package (The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). The prevalence of clinical signs among severe (cases) and non-severe dengue cases (controls) over the course of the disease was compared using the Pearson χ^2 test in addition to the odds ratio (OR) calculation (95% confidence interval – 95%CI). Additionally, we carried out a descriptive analysis of cases and controls according to the variable received medical assistance and day of hospitalization for severe cases over the course of the disease.

Ethical approval

The project was approved by the Research Ethics Committees of the City of Rio de Janeiro Municipal Health Secretary (ruling number 0029.0.314.011-09), the IPPMG/UFRJ (ruling number 03/09) and the Evandro Chagas Institute of Clinical Research – IPEC/Fiocruz, acronym in Portuguese (ruling number 061/2008).

Results

We collected 455 samples of serum during household interviews from 88 children classified as severe hospitalized cases and 367 possible neighboring controls. The median age of both cases and possible controls was 10 years and Pearson's χ^2 test revealed that there were no statistically significant differences with respect to sex and age between these two groups (p-value = 0.295 and p-value = 0.376).

Laboratory results

Of the possible controls that reported never having dengue fever (340), 193 tested positive and 128 tested negative for IgG-class immunoglobulins; tests were not conclusive for 19 individuals. Thus serological testing showed that 87.7% (193/193+27) of dengue infections among possible controls were asymptomatic or oligosymptomatic and that 12.2% (27/193+27) were symptomatic (Table 1).

Prevalence of asymptomatic/oligosymptomatic infections among possible controls decreased with increasing age. One hundred per cent (6/6) of previous dengue infections in children under five years of age were asymptomatic or oligosymptomatic. This proportion reached 92.3% (84/84+7) in the six to ten years age group, while among children and adolescents in the eleven to eighteen years age group prevalence of asymptomatic/oligosymptomatic infections reached 83.7% (103/103+20) (Table 1).

Clinical evolution

Comparative analysis of daily symptomatic manifestations among severe cases and controls with non-severe dengue (not admitted to hospital) performed using the Pearson χ^2 test showed that on the first two days of the disease there were no statistically significant differences with respect to the prevalence of clinical signs (fever, abdominal pain, bleeding episodes, drowsiness/ irritability and breathing difficulty). Differences occurred on the third, fourth and fifth days of the disease (Table 2).

On the third day of the disease, severe cases were 5.92 times more likely to have fever (p = 0.002). The same positive association was observed for abdominal pain and breathing difficulty, where severe cases were 5.07 (p = 0.002) and 9.69 (p = 0.01) times more likely to display these symptoms than non-severe cases (controls), respectively. On the fourth day of the disease the likelihood of displaying symptoms such as fever and abdominal pain remained greater (OR = 13.29; p < 0.001 and OR = 6.92; p = 0.004, respectively) among severe cases when compared with the control group. The same was observed for the symptoms irritability and/or drowsiness, which were 9.93 times more likely to appear in severe cases than in the control group (p = 0.001). On the other hand, on the fifth day after the onset of the disease the only symptom that was statistically higher among severe cases was irritability and/or drowsiness, being 10.6 times more likely (p = 0.003) in this group. We did not observe significant differences in self-reported previous dengue infection between the groups (Table 2).

Regarding first medical assistance received by patients, no statistically significant difference was found between severe cases and non-severe controls. According to Figure 1, by the third day after onset of the disease 100% of controls had received some form of medical assistance. Of the 22 controls with non-severe dengue, 14 (63.6%) received medical assistance on the first day of the disease, while five (22.7%) and three individuals (13.6%) received first medical assistance only on the second and third day of symptoms, respectively (Figure 1). Regarding the type of care provided, 19 (86.3%) of the 22 controls received first medical assistance at primary health care units of the Brazilian Unified National Health System (SUS, acronym in Portuguese), while three (13.6%) were initially treated in private health care clinics.

Among severe cases, 85 of the 88 patients (96.6%) had received first medical assistance by the third day after the onset of the disease; 58 (65.9%) received assistance on first day, 21 (23.9%) on the second day and only six (6.8%) on the third day after the onset of the disease. It is important to highlight that three cases received medical assistance on the fourth, seventh and ninth day, respectively, after the onset of the disease (Figure 1). With regard to the type of care provided, 67 patients (76.1%) received their first medical assistance at primary healthcare units of the SUS, while 21 (23.8%) were initially treated in private health care clinics.

With respect to hospital admissions, we verified that 50% of severe cases (44) were hospitalized by the third day after the onset of the disease. On the first day of onset only two cases (2.3%) were hospitalized, while on the second, third and fourth days 16 (18.2%), 26 (29.5%) and 14 (15.9%) were hospitalized, respectively. The second highest percentage of hospital admissions occurred on the fifth day (19 cases or 21.6% of the sample). Six patients (6.8%) were hospitalized on the sixth day and four (4.5%) on the seventh day. It should be highlighted that one case was hospitalized on the ninth day after the onset of symptoms (Figure 2).

Discussion

When comparing severe (cases) and non-severe (controls) dengue cases, no significant difference was found with regard to the time taken to receive medical assistance. This fact suggests that on average both groups received their first medical assistance at the same time during the clinical

Table 1

Distribution of possible controls according to age group and IgG serological test for dengue virus.

Age group (years)	Reported never having dengue Serology (IgG)			Reported having dengue before Serology (IgG)			Total
	Positive	Negative	Inconclusive	Positive	Negative	Inconclusive	
≤ 5	6	34	0	0	0	0	40
6-10	84	64	12	7	0	0	167
11-18	103	30	7	20	0	0	160
Total	193	128	19	27	0	0	367

Table 2

Frequency of clinical symptoms in dengue fever cases (severe and non-severe) and non-adjusted odds ratio (OR) according to the daily evolution of the disease. Rio de Janeiro, Brazil, 2007-2008.

Associated clinical symptoms	Severe dengue		Non-severe dengue		OR	95%CI	p-value
	n	%	n	%			
3rd day of symptoms							
Fever	78	91.7	11	64.7	5.92	1.38-25.26	0.002
Abdominal pain	62	73.8	6	35.3	5.07	1.51-18.84	0.002
Shortness of breath	32	38.1	1	5.9	9.69	1.38-424.74	0.010
4th day of symptoms							
Fever	64	95.5	6	60.0	13.29	1.81-114.04	0.000
Abdominal pain	49	75.3	3	30.0	6.92	1.38-46.38	0.004
Irritability/Drowsiness	63	94.0	6	60.0	9.93	1.47-69.96	0.001
5th day of symptoms							
Irritability/Drowsiness	46	93.9	3	50.0	10.6	1.08-110.84	0.003
Variables							
Previous infection report	3	3.4	2	9.1	0.36	0.04-4.54	0.252

95%CI: 95% confidence interval.

course of the disease. This finding reduces the likelihood of negative prognosis due to a delay in providing initial care. It is important to highlight that controls resided in the same neighborhood as the cases, meaning that the two groups have similar characteristics in terms of socioeconomic status, access to healthcare services and exposure to the virus [19,20].

A descriptive analysis of hospital admissions among severe cases suggests that hospitalizations occurred between the third and fourth days after onset of the disease, in the febrile phase, after receiving first medical assistance at primary health care units. Although dengue may have been diagnosed during the first medical assistance, sufficient emphasis may not have been given to the importance of observing warning signs when ad-

vising parents and this may have contributed to inadequate observation of signs and consequent delay in seeking emergency care.

Similarly, the possible lack of recognition of warning signs by health professionals could have contributed to early discharge of potentially severe patients, in situations where it would be necessary to keep them under close clinical observation.

Furthermore, the early and unexpected presence of symptoms of severe dengue (abdominal pain, breathing difficulty and irritability/drowsiness) in the febrile phase of the disease may have caused difficulties in triage of patients and risk classification. The concurrence of these symptoms with fever is atypical, since, in general, the clinical symptoms of severe dengue in adults

Figure 1

Clinical evolution of severe and non-severe dengue cases by day after the onset of symptoms, Rio de Janeiro, Brazil, 2007-2008.
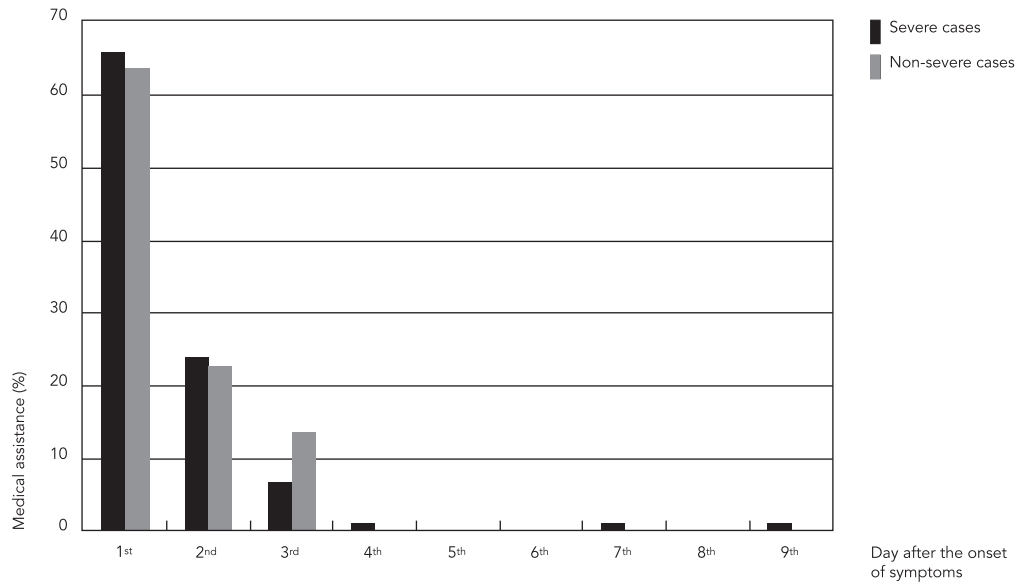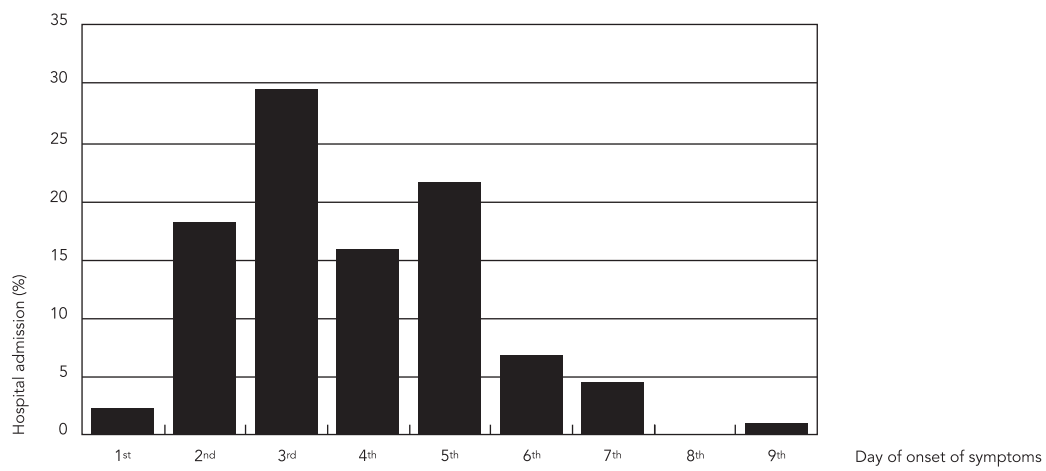

Figure 2

Hospital admissions of severe cases during the clinical course of the disease, Rio de Janeiro, Brazil.

usually occur in the absence of fever or during defervescence. Therefore, this finding reveals a difference among young age groups, where pre-ceding symptomatic manifestations often occur during the febrile phase [16,21]. This scenario reflects the need for further studies about clinical

signs in children, especially those under the age of five years.

Although the new classification of dengue proposed by the World Health Organization (WHO) [18] lists several clinical and laboratory warning signs, the traditional WHO classification [22] is the most widely used in daily practice. This classification emphasizes hemorrhage, because of the term hemorrhagic dengue fever and/or thrombocytopenia, as opposed to signs of capillary extravasation, which are responsible for the severe form of disease [23]. This could lead to the early discharge of patients not showing signs of hemorrhaging and/or thrombocytopenia and who are seeking medical care for the first time, resulting in the return of these patients presenting symptoms of severe dengue. With respect to severe cases, it is important to highlight that only "hemorrhagic manifestations" were not significantly more prevalent among the clinical symptoms analyzed throughout the daily evolution of the disease. On the other hand, this is a non-specific variable relating to hemorrhagic manifestations that are often associated with severe conditions, thus contributing to the lack of a significant association. Furthermore, the fact that there is greater prevalence of irritability and/or drowsiness, shortness of breath and abdominal pain among severe cases on the third day (when the majority of severe cases had not yet been hospitalized) stresses the importance of these signs as prognostic predictors. The recognition of these symptoms as warning signs may be useful for prioritizing medical care [24] during triage of patients and risk classification, especially in health care units that have limited resources.

The capillary leak syndrome caused by an increase in vascular endothelial permeability may manifest itself initially with the appearance of warning signs such as abdominal pain and respiratory distress. These are the main initial symptoms reported by severe cases which, if not appropriately treated by intravenous hydration and continuous monitoring during the critical phase of the disease may lead to tissue hypoperfusion and shock (criteria used to define severe cases).

Although consecutive infections with different serotypes are often highlighted as one of the main risk factors for severe dengue [4,24], in this study we did not observe a significant association between history of previous dengue infections and severity. However, it should be noted that previous dengue infection was self-reported by participants during interviews, which means that only symptomatic infections were counted. Indeed, the results of the serological analysis of IgG among possible controls that did not report previous dengue episodes showed a high prevalence of positive serology (87.7%) – asymptomatic/oligosymptomatic infections- suggesting the existence of a silent source of transmission.

Our results should be interpreted with caution, considering the inherent limitation of retrospective studies due to memory bias. The possibility of unreliable reporting of the daily clinical evolution of the disease by mothers of severe cases may lead to an overestimate of associations.

Another limitation of this study is the small number of controls, which contributed to an increase in the confidence intervals and a resulting reduction in the accuracy of ORs. This does not however invalidate our results, but corroborates findings of the scientific literature regarding this matter and adds to the discussion concerning the role primary health care plays in the clinical outcome of patients with dengue.

Despite issues involving statistical power, statistically significant ORs emphasize the importance of certain clinical symptoms as predictors of severity. Although abdominal pain is a frequent and non-specific complaint among children [3], our study was able to demonstrate the prognostic value of this symptom and emphasize its importance as a warning sign mentioned by the WHO [18] that warrants careful investigation in children with a confirmed diagnosis of dengue fever.

Conclusions

Recurrent dengue epidemics in Rio de Janeiro and the rest of Brazil have lead to a disruption of routine health services, therefore demanding further efforts towards providing technical training to health professionals working on the frontline of dengue patient care. These professionals must be trained to strictly follow the risk classification protocol and perform clinical evaluations at short time intervals. Additionally, as we showed in our results, primary health care units play an important role in patient triage and must be prioritized, especially during epidemic periods [20,25]. Considering that recovery from dengue is possible for the majority of individuals, the current challenge is to identify the small minority of patients whose condition may potentially progress to severe forms of the disease and would therefore be at imminent risk of death in the absence of appropriate and timely clinical management. Furthermore, advanced planning in the health care network and awareness among health professionals of the possibility of an epidemic are essential to ensure an effective diagnosis of dengue at the first medical appointment.

Resumen

Fueron evaluados factores asociados a la ocurrencia de casos graves de dengue en niños/adolescentes hospitalizados, durante la epidemia de 2007/2008 en Río de Janeiro, Brasil. Se trata de un estudio caso-control retrospectivo con 88 casos graves de dengue, admitidos en cuatro hospitales de atención terciaria infantil. Los controles se efectuaron con 22 niños con dengue no grave, residentes en los alrededores de los casos. Se observaron diferencias en la prevalencia de señales clínicas –dolor abdominal, dificultad respiratoria, somnolencia/irritabilidad– a partir del tercer día del inicio de los síntomas, todavía con presencia de fiebre. Casos y controles recibieron la primera atención médica en la misma fase clínica de la enfermedad. No obstante, las hospitalizaciones de los casos graves se produjeron más tardíamente, en media entre el tercer y cuarto día de la enfermedad. El alta precoz de pacientes con cuadro febril, y potencialmente graves, puede haber sido consecuencia de la atención médica prestada en las unidades de atención primaria, sugiriendo deficiencias en la aplicación del protocolo de clasificación de riesgo de dengue y selección de pacientes.

Dengue; Epidemias; Signos y Síntomas

Contributors

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